The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.23(3H, d), 2.16(3H, s), 2.84(3H, s), 2.87-2.95(2H, m), 3.03(3H, s), 3.15-3.24(2H, m), 3.56(1H, s), 4.78(3H, t, J=7.0 Hz), 7.13(2H, d, J=8.4 Hz), 7.25(2H, d, J=8.4 Hz), 8.09(1H, d, J=7.0 Hz), 9.67(1H, s), 12.35(1H, s).

MS: 446(M+H)$^+$ free

Production Example 94: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[(1S)-1-benzyl-2-(dimethylamino)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[(1S)-1-benzyl-2-(dimethylamino)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.48(9H, s), 1.52(9H, s), 2.22(3H, s), 2.68(3H, s), 2.84-2.97(5H, m), 3.06(2H, d, J=7.5 Hz), 3.17(H, dd, J=8.0, 6.0 Hz), 5.26(1H, q, J=7.5 Hz), 6.80(1H, d, J=8.0 Hz), 7.08(2H, d, J=8.0 Hz), 7.14-7.33(5H, m), 7.39(2H, d, J=8.0 Hz), 9.96(1H, br), 10.19(1H, s), 11.61(1H, s).

MS: 722(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.15(3H, s), 2.82-3.15(13H, m), 4.91(1H, q, J=6.7 Hz), 7.09(4H, s), 7.16-7.31(5H, m), 7.36(4H, br), 8.31(1H, d, J=7.7 Hz), 9.71(1H, s), 12.33(1H, s).

MS: 522(M+H)$^+$ free

Production Example 95: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[(1S)-2-(dimethylamino)-1-(hydroxymethyl)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[(1S)-2-(dimethylamino)-1-(hydroxymethyl)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.48(9H, s), 1.52(9H, s), 2.23(3H, s), 2.94(2H, dd, J=7.0 Hz), 3.01(3H, s), 3.14(3H, s), 3.26(2H, dd, J=7.0 Hz), 3.78-3.86(3H, br), 5.04(1H, m), 6.85(1H, d, J=7.5 Hz), 7.08(2H, d, J=8.5 Hz), 7.37(2H, d, J=8.5 Hz), 9.70(1H, br), 10.20(1H, s), 11.61(1H, s).

MS: 662(M+H)$^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.16, 2.19(3H, s x2), 2.85-3.50(10H, m), 3.60-3.69(2H, m), 4.81(1H, m), 7.14(2H, m), 2.27(2H, m), 7.39(4H, br), 7.91(1H, br), 8.48(1H, br), 9.77, 9.94(1H, s x2), 12.37, 12.61(1H, s x2).

MS: 462(M+H)$^+$ free

Production Example 96: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-{(1S,2S)-1-[(dimethylamino)carbonyl]-2-hydroxypropyl}-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[({(1S,2S)-1-[(dimethylamino)carbonyl]-2-hydroxypropyl}amino)carbonyl]-

1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.18(3H, d, J=6.5 Hz), 1.48(9H, s), 1.52(9H, s), 2.22(3H, s), 2.95(2H, m), 2.99(3H, s), 3.16(3H, s), 3.20-3.32(2H, m), 4.06-4.12(2H, m), 5.02(1H, dd, J=9.0, 1.5 Hz), 6.55(1H, d, J=9.0 Hz), 7.09(2H, d, J=8.0 Hz), 7.38(2H, d, J=8.0 Hz), 9.70(1H, br), 10.20(1H, s), 11.62(1H, s).

MS: 676$(M+H)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.35(3H, d, J=6.5 Hz), 2.19(3H, s), 2.85-2.97(6H, m), 3.11(3H, s), 3.26(2H, m), 4.67(1H, br), 5.40(1H, m), 7.15(2H, d, J=8.3 Hz), 7.28(2H, d, J=8.3 Hz), 7.43(4H, br), 8.43(3H, br), 9.93(1H, s), 12.59(1H, s).

MS: 475$(M+H)^+$ free

Production Example 97: Synthesis of (2S)-2-[({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)amino]-N^1,N^1-dimethylpentanediamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[({(1S)-4-amino-1-[(dimethylamino)carbonyl]-4-oxobutyl}amino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s), 1.86-2.19(2H, m), 2.22-2.37(5H, m), 2.89(2H, m), 2.99(3H, s), 3.05-3.16(5H, m), 3.20-3.41(1H, m), 5.06(1H, m), 6.27(1H, br),

6.35(1H, br), 6.81(1H, d, J=7.5 Hz), 7.09(2H, d, J=8.5 Hz), 7.41(2H, d, J=8.5 Hz), 10.21(1H, s), 10.55(1H, br), 11.62(1H, s).

MS: 703 $(M+H)^+$

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.70-2.00(2H, m), 2.16(5H, m), 2.84(3H, s), 2.91(2H, m), 3.08(3H, s), 3.19(2H, m), 4.75(1H, m), 6.79(1H, m), 7.12(2H, d, J=8.3 Hz), 7.25(2H, d, J=8.3 Hz), 7.39(4H, br), 8.13(1H, d), 9.77(1H, s), 12.35(1H, s).

MS: 503 $(M+H)^+$ free

Production Example 98: Synthesis of N-{4-[2-(4-{[imino(methylamino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

The title compound was prepared from the compound obtained in Step 2 of Production Example 50 in a similar manner according to Production Example 58.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.79(3H, s), 2.86(4H, s), 3.18(3H, s), 4.08(2H, s), 4.43(2H, m), 7.08(2H, d, J=8.5Hz), 7.22(2H, d, J=8.5Hz), 7.39(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz), 12.05(1H, brs).

MS: 486 $(M+H)^+$

Production Example 99: Synthesis of (2S)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N,N-dimethyl-2-pyrrolidinecarboxamide dihydrochloride

Step 1

tert-Butyl {4-[2-(2-(acetylamino)-5-{[methoxy(methyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-

5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.74-2.93(2H, m), 3.12-3.29(2H, m), 3.22(3H, s), 3.59(3H, s), 7.05(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 9.21(1H, s), 12.34(1H, s).

MS: 471.1$(M+Na)^+$

Step 2

To a solution of the compound obtained in Step 1 (3.93 g) in THF (80 mL) was added lithium aluminium hydirde (499 mg) slowly (over 15 min) at 5-10°C (under ice-cooling). The mixture was stirred at 5°C for 1 h. 30 mL of aqueous solution of potassium sodium tartrate (1M) was added slowly under ice-cooling, and then the mixture was stirred for another 0.5 h at r.t. The mixture was extracted with ethyl acetate, and the organic layer was dried over $MgSO_4$, and concecntrated *in vacuo* to give pale yellow oil. This oil was triturated with IPE and EtOAc to give tert-butyl (4-{2-[2-(acetylamino)-5-formyl-1,3-thiazol-4-yl]ethyl}phenyl)carbamate as pale yellow powder (2.67g).

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.46(9H, s), 2.19(3H, s), 2.90(2H, t, J=7.3 Hz), 3.22(2H, t, J=7.3 Hz), 7.01(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 9.22(1H, s), 9.77(1H, s), 12.68(1H, s).

MS: 390$(M+H)^+$

Step 3

To a solution of the compound obtained in Step 2 (200 mg) in dichloromethane (6 mL) were added (2S)-2-(N,N-dimethylaminocarbonyl)pyrrolidine hydrochloride and diisopropylethylamine (0.27 ml) at 5°C. The mixture was stirred at 5°C for 10 min. Then sodium triacetoxyborohydride (327 mg) was added, and the mixture was stirred for 3 hrs. aq. NH_4Cl was added, and the mixuture was extracted with

dichloromethane. The organic layer was dried over $MgSO_4$. The layer was concentrated under reduced pressure. The resulting crude mixture was purified by silica gel column chlomatography with mixed solvent (dichloromethane/methanol=15/1) as an eluent to give tert-butyl (4-{2-[2-(acetylamino)-5-({(2S)-2-[(N,N-dimethylamino)carbonyl]-1-pyrrolidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate as a pale yellow amorphous substance.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.67-1.99(4H, m), 2.24(3H, s), 2.04(4H, s), 2.14(3H, s), 2.95-3.14(5H, m), 3.42-3.58(2H, m), 3.68-3.83(1H, m), 6.97(2H, d, J=8.3 Hz), 7.94(2H, d, J=8.3 Hz).

MS: 516$(M+H)^+$

Step 4

(2S)-1-({2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N,N-dimethyl-2-pyrrolidinecarboxamide was prepared in a similar manner according to Step 2 of Production Example 31.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.70-2.10(4H, m), 2.22(3H, s), 2.39(1H, q, J=8.4 Hz), 2.77(4H, m), 2.91(3H, s), 3.03(3H, s), 3.30-3.81(6H, m), 6.58(2H, d, J=8.3 Hz), 6.89(2H, d, J=8.3 Hz), 8.82(1H, br).

MS; 416$(M+H)^+$

Step 5

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(2S)-2-[(N,N-dimethylamino)carbonyl]-1-pyrrolidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.50(9H, s), 1.52(9H, s), 1.76-1.92(4H, m), 2.04-2.14(1H, m), 2.43(1H, dd, J=8.1, 8.0 Hz), 2.45(3H, s), 2.85(2H, s), 3.07(3H, s), 3.51(1H, dd, J=5.7, 8.0 Hz), 3.60(1H, d, J=14.3 Hz), 3.84(1H, d, J=14.3

Hz), 6.37(1H, t, J=2.0 Hz), 7.08(2H, d, J=8.4 Hz), 7.44(2H, d, J=8.4 Hz), 7.63(1H, d, J=2.0 Hz), 10.23(1H, s), 11.62(1H, br).
MS: 658(M+H)$^+$

Step 6

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.
^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 1.60-1.98(2H, br), 1.98-2.16(1H, br), 2.16(3H, s), 2.85(3H, s), 2.95(7H, br), 3.00-3.30(1H, br), 7.15(2H, d, J=8.3 Hz), 7.30(2H, d, J=8.3 Hz), 7.55(4H, br), 7.85(1H, d, J=2.2 Hz), 9.65(1H, br), 10.21(1H, s), 12.35(1H, s).
MS: 458(M+H)$^+$ free

Production Example 100: Synthesis of 3-[({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)(methyl)amino]-N,N-dimethylpropanamide dihydrochloride

Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[3-(N,N-dimethylamino)-3-oxopropyl]amino}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from the compound obtained in Step 2 of Production Example 99 in a similar manner according to Step 3 of Production Example 99.
^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.50(9H, s), 2.24(3H, s), 2.47(2H, t, J=6.2 Hz), 2.74(2H, t, J=6.2 Hz), 2.82-2.88(4H, m), 2.93(3H, s), 2.97(3H, s), 3.59(2H, s), 6.94(2H, d, J=8.3 Hz), 7.21(2H, d, J=8.3 Hz), 8.02(1H, s).
MS: 490(M+H)$^+$

Step 2

To a solution of the compound obtained in Step 1 (100 mg) in dichloromethane (1.5 mL) was added formaline (35%, 87.6 μl). To this suspension was added 0.05 ml of MeOH. Then, sodium triacetoxyborohydride (433 mg) was added, and the mixture was stirred for 12 hrs. To the mixture were added water and 1N

NaOH to adjust pH of aqueous phase (ca. pH 8-9). The mixture was extracted with dichloromethane. The organic layer was dried with $MgSO_4$ and concentrated under redused pressure. Resulting oil was purified by silica gel column chromatography (mixed solvent of CH_2Cl_2/MeOH 15/1 as an eluent) to give tert-butyl {4-[2-(2-(acetylamino)-5-{[[3-(N,N-dimethylamino)-3-oxopropyl](methyl)amino]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate as pale yellow oil (90.4 mg).

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.51(9H, s), 2.18(3H, s), 2.24(3H, s), 2.45(2H, m), 2.62(2H, m), 2.80(4H, s), 2.93(3H, s), 2.99(3H, s), 3.35(2H, s), 6.96(2H, d, J=8.3 Hz), 7.20(2H, d, J=8.3 Hz).

MS: 504$(M+H)^+$

Step 3

3-[({2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-5-yl}methyl)(methyl)amino]-N,N-dimethylpropanamide was prepared in a similar manner according to Step 2 of Production Example 31.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 2.19(3H, s), 2.22(2H, s), 2.43-2.51(2H, m), 2.62-2.71(4H, m), 2.78(3H, s), 2.93(3H, s), 2.99(3H, s), 3.33(2H, s), 3.65(1H, m), 3.75(1H, m), 6.58(2H, d, J=8.3 Hz), 6.87(2H, d, J=8.3 Hz).

MS: 404$(M+H)^+$

Step 4

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[[3-(N,N-dimethylamino)-3-oxopropyl](methyl)amino]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR (200MHz, $CDCl_3$), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.20(3H, s), 2.22(3H, s), 2.49(2H, dd, J=6.5, 5.5 Hz), 2.71(2H, dd, J=6.5, 5.5 Hz), 2.84(4H, s), 2.93(3H, s), 2.99(3H, s), 3.43(2H, s), 7.08(2H, d, J=8.4 Hz), 7.46(2H, d,

J=8.4 Hz), 7.62(1H, s), 10.24(1H, s), 11.62(1H, s).

MS: 646(M+H)$^+$

Step 5

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200MHz, DMSO-d_6), δ (ppm): 2.15(3H, s), 2.68(3H, d, J=4.0 Hz), 2.83-2.88(6H, m), 2.96(6H, s), 3.05-3.15(2H, m), 4.44(2H, m), 7.15(2H, d, J=8.3 Hz), 7.32(2H, d, J=8.3 Hz), 7.62(4H, br), 9.90(1H, s), 12.32(1H, s).

MS: 446(M+H)$^+$ free

Production Example 101: Synthesis of 4-(2-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}ethyl)-N,N-dimethylbenzamide hydrochloride

Step 1

Methyl 4-{2-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]vinyl}benzoate was prepared from the compound obtained in Step 2 of Production Example 99 in a similar manner according to Step 1 of Production Example 53.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9Hx4/9, s), 1.51(9Hx5/9, s), 2.20(3Hx5/9, s), 2.29(3Hx4/9, s), 2.72-3.06(4H, m), 3.90(3Hx5/9, s), 3.92(3Hx4/9, s), 6.42-6.60(2Hx5/9, m), 6.69(1Hx4/9, d, J=16.6Hz), 6.81-7.03(4H + 1Hx4/9, m), 7.31(2Hx5/9, d, J=8.0Hz), 7.39(2Hx4/9, d, J=8.0Hz), 7.96(2Hx5/9, d, J=8.0Hz), 7.99(2Hx4/9, d, J=8.0Hz).

MS: 522.2(M+H)$^+$, 544.2(M+Na)$^+$

Step 2

Methyl 4-{2-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]ethyl}benzoate was prepared in a similar manner according to Step 6 of Production Example 45.

MS: 524.25(M+H)$^+$

Step 3

4-{2-[2-(Acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]ethyl}benzoic acid was prepared in a similar manner according to Step 2 of Production Example 65.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.45(9H, s), 2.09(3H, s), 2.57-2.72(6H, m), 2.75-2.86(2H, m), 6.94(2H, d, J=8.4Hz), 7.21(2H, d, J=8.4Hz), 7.32(2H, d, J=8.4Hz), 7.82(2H, d, J=8.4Hz), 9.21(1H, s), 11.94(1H, s), 12.41-13.20(1H, brs).

MS: 510.2(M+H)$^+$, 532.2(M+Na)$^+$

Step 4

tert-Butyl (4-{2-[2-(acetylamino)-5-(2-{4-[(methylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared in a similar manner according to Step 3 of Production Example 65.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.51(9H, s), 2.24(3H, s), 2.56-2.73(4H, m), 2.73-2.86(4H, m), 2.99(3H, d, J=4.8Hz), 6.05(1H, d, J=4.4Hz), 6.25-6.75(1H, brs), 6.77(2H, d, J=6.6Hz), 7.12(2H, d, J=8.1Hz), 7.15-7.23(2H, m), 7.63(2H, d, J=8.1Hz), 8.43-9.18(1H, brs).

MS: 523.29(M+H)$^+$

Step 5

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(2-{4-[(methylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 4 of Production Example 65.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.48(9H, s), 1.54(9H, s), 2.22(3H, s), 2.51-2.61(2H, m), 2.61-2.71(2H, m), 2.79-2.90(4H, m), 2.97(3H, d, J=4.8Hz), 6.20(1H, d, J=4.8Hz), 6.98(2H, d, J=8.4Hz), 7.13(2H, d, J=8.1Hz), 7.40(2H, d, J=8.4Hz), 7.64(2H, d, J=8.4Hz), 8.83-9.42(1H, brs), 10.21(1H,s), 11.62(1H, s).

MS: 687.2(M+Na)$^+$

Step 6

The title compound was prepared in a similar manner

according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.58-2.79(6H, m), 2.80-3.02(8H, m), 7.13(2H, d, J=8.4Hz), 7.19(2H, d, J=8.1Hz), 7.20(2H, d, J=8.4Hz), 7.29(2H, d, J=8.1Hz), 7.32(4H, s), 9.66(1H, s), 11.93(1H, s).

MS: 479.2(M+H)$^+$ free

Production Example 102: Synthesis of 4-(2-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}ethyl)-N-methylbenzamide hydrochloride

Step 1

tert-Butyl (4-{2-[2-(Acetylamino)-5-(2-{4-[(dimethylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from the compound obtained in Step 3 of Production Example 101 in a similar manner according to Step 3 of Production Example 65.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.51(9H, s), 2.23(3H, s), 2.66(4H, s), 2.79(4H, s), 2.93(3H, s), 3.08(3H, s), 6.90(2H, d, J=8.0Hz), 7.11(2H, d, J=8.0Hz), 7.18(2H, d, J=8.0Hz), 8.56-10.01(1H, brs).

MS: 537(M+H)$^+$, 559.2(M+Na)$^+$

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(2-{4-[(dimethylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 4 of Production Example 65.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.21(3H, s), 2.57-2.78(4H, m), 2.82(4H, s), 2.94(3H, s), 3.08(3H, s), 7.03(2H, d, J=8.5Hz), 7.13(2H, d, J=8.0Hz), 7.33(2H, d, J=8.0Hz), 7.45(2H, d, J=8.5Hz), 8.28-9.61(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 679.2(M+H)$^+$, 701.2(M+Na)$^+$

Step 3

The title compound was prapared in a similar manner

according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3H, s), 2.60-2.72(4H, m), 2.72-2.80(2H, m), 2.76(3H, d, J=4.4Hz), 2.89(2H, t, J=7.3Hz), 7.12(2H, d, J=8.4Hz), 7.19(2H, d, J=8.4Hz), 7.22(2H, d, J=8.1Hz), 7.33(4H, s), 7.73(2H, d, J=8.1Hz), 8.36(1H, d, J=4.4Hz), 9.66(1H, s), 11.93(1H, s).

MS: 465.2(M+H)$^+$ free

Production Example 103: Synthesis of methyl N—[4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)phenyl]carbamate hydrochloride

Step 1

To a suspension of 4-{[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}benzoic acid (50 mg) in toluene (0.5 ml) and dioxane (0.5 ml) were added triethylamine (28.1 μl) and diphenylphosphoryl azide (39.1 μl), and the mixture was stirred at 25°C for 2 hrs., then stirred at 100°C for 1 h. To the reaction mixture was added methanol (1 ml), and the mixture was refluxed for 2 hrs., and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give methyl N-(4-{[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}phenyl)carbamate (17.2 mg).

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.52(9H, s), 2.22(3H, s), 2.80(4H, s), 3.76(3H, s), 3.79(2H, s), 6.62-6.78(1H, brs), 6.83-7.05(1H, brs), 6.90(2H, d, J=8.0Hz), 6.98(2H, d, J=8.5Hz), 7.17(2H, d, J=8.0Hz), 7.20-7.33(2H, m).

MS: 547.2(M+Na)$^+$

Step 2

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{4-[(methoxycarbonyl)amino]benzyl}-1,3-thiazol-4-

yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 4 of Production Example 65.
^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.54(9H, s), 2.19(3H, s), 2.82(4H, s), 3.76(3H, s), 3.80(2H, s), 6.72-6.90(1H, brs), 6.98(2H, d, J=8.5Hz), 7.00(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz), 7.39(2H, d, J=8.5Hz), 9.10-9.59(1H, brs), 10.19(1H, s), 11.64(1H, s).
MS: 667.2(M+H)$^+$, 689.2(M+Na)$^+$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.
^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3H, s), 2.85(4H, s), 3.64(3H, s), 3.85(2H, s), 7.04(2H, d, J=8.5Hz), 7.14(2H, d, J=8.4Hz), 7.24(2H, d, J=8.4Hz), 7.28-7.47(6H, m), 9.58(1H, s), 9.70(1H, s), 11.96(1H, s).
MS: 467.2(M+H)$^+$

Production Example 104: Synthesis of ethyl 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-4-piperidinecarboxylate dihydrochloride

Step 1

Ethyl 1-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl}methyl)-4-piperidinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.
MS: 459.17(M+H)$^+$

Step 2

Ethyl 1-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-4-piperidinecarboxylate was prepared in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.24(3H, t, J=7.2Hz), 1.50(9H, s), 1.53(9H, s), 1.65-2.09(6H, m), 2.13-2.34(4H, s), 2.71-2.95(6H, m), 3.39(2H, s), 4.12(2H, q, J=7.2Hz), 7.07(2H, d, J=8.5Hz), 7.46(2H, d, J=8.5Hz), 10.24(1H, s), 11.63(1H, brs).

MS: 673.3(M+H)$^+$, 695.3(M+Na)$^+$

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.18(3H, t, J=7.1Hz), 1.73-1.90(2H, m), 1.93-2.13(2H, m), 2.16(3H, s), 2.87-3.01(6H, m), 3.30-3.41(2H, m), 4.08(2H, q, J=7.1Hz), 4.31-4.43(2H, m), 7.15(2H, d, J=8.4Hz), 7.31(2H, d, J=8.4Hz), 7.42(4H, s), 9.90(1H, s), 10.23-10.46(1H, brs), 12.3(1H, s).

MS: 473.2(M+H)$^+$, 495.2(M+Na)$^+$ free

Production Example 105: Synthesis of ethyl 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-4-piperidinecarboxylate hydrochloride

The title compound was prepared in a similar manner according to Example 104.

Production Example 106: Synthesis of 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)-N-[amino(imino)methyl]benzamide

Guanidine hydrochloride (152 mg) was dissolved in DMF (3 ml), and then 28 % sodium methoxide methanol solution (0.3 ml) was added to the solution at r.t. The suspension was stirred at r.t. for 15 minutes, and methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)benzoate (150 mg) was added to the mixture at r.t. The reaction mixture was stirred at r.t. for 14 hours, and concentrated *in vacuo*. The residue was dissolved in water, and neutralized with 1N-HCl. The precipitate was collected through filtration, and purified by preparative silica gel chromatography with $CHCl_3$ / MeOH

(10:1) as an eluent. The solid was washed with ethyl ether to give 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)-N-[amino(imino)methyl]benzamide (36.6 mg) as an off-white solid.

mp. 108-109.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.89(4H, s), 3.16(3H, s), 4.06(2H, s), 7.15(2H, d, J=8.0Hz), 7.27(2H, d, J=8.0Hz), 7.78(2H, d, J=8.0Hz), 7.95(2H, d, J=8.0Hz), 12.04(1H, s).

MS: 500(M+H)$^+$

Production Example 107: Synthesis of tert-butyl (2-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}-2-oxoethyl)carbamate

The title compound was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol in a similar manner according to Step 1 of Production Example 10.

mp. 186-187.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.39(9H, s), 2.08(3H, s), 2.84(4H, s), 3.17(3H, s), 3.71(2H, d, J=6.0Hz), 4.00(2H, s), 7.01(1H, t, J=6.0Hz), 7.06(2H, d, J=8.5Hz), 7.28(2H, d, J=8.5Hz), 7.46(2H, d, J=8.5Hz), 7.79(2H, d, J=8.5Hz), 9.86(1H, s), 12.04(1H, s).

MS: 587(M+H)$^+$

Production Example 108: Synthesis of N-[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]-2-aminoacetamide hydrochloride

The title compound was prepared from the compound of Production Example 107 in a similar manner according to Step 2 of Production Example 10.

mp. 142.5-144°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.09(3H, s), 2.85(4H, s), 3.18(3H, s), 3.78(2H, m), 4.00(2H, s), 7.10(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz), 7.50(2H, d, J=8.5Hz), 7.79(2H, d, J=8.5Hz),

8.22(3H, brs), 10.63(1H, s), 12.06(1H, s).

MS: 487(M+H)$^+$ free

Production Example 109: Synthesis of N-(4-{2-[4-(2-aminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride

Step 1

N-(4-{2-[4-(Cyanomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (1 g), 1N-NaOH (7 ml) and EtOH (14 ml) were combined, and the reaction mixture was refluxed for 8 hours. After cooled to r.t., the organic solvent was removed *in vacuo*. The aqueous solution was neutralized with 1N-HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual yellow wax (1.03 g) was dissolved in THF (10 ml), and then lithium aluminium hydride (266 mg) was added to the solution at 0°C. The reaction mixture was refluxed for 3 hours, and quenched with MeOH. Then Na_2SO_4 / $10H_2O$ was added to the mixture, the mixture was stirred at r.t. for 1 hour and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residual yellow amorphous (835.5 mg) was dissolved in THF (10 ml) and DMF (10 ml) under N_2 atmosphere. Then di(tert-butyl) dicarbonate (841 mg) in THF (5 ml) was added to the solution at r.t. The reaction mixture was stirred at r.t. for 12 hours, and concentrated *in vacuo* to give tert-butyl (2-{4-[2-(2-amino-1,3-thiazol-4-yl)ethyl]phenyl}ethyl)carbamate (171.6 mg) as yellow oil.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.38(9H, s), 2.60-2.70(4H, m), 2.79-2.88(4H, m), 6.82(1H, s), 7.07(2H, d, J=8.0Hz), 7.11(2H, d, J=8.0Hz).

MS: 348(M+H)$^+$

Step 2

tert-Butyl [2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl]carbamate was prepared from the compound

of Step 1 in a similar manner according to Step 3 of Production Example 45.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.36(9H, s), 2.11(3H, s), 2.58-2.70(1H, m), 2.80-2.97(6H, m), 3.02-3.18(1H, m), 6.72(1H, s), 7.08(2H, d, J=8.0Hz), 7.23(2H, d, J=8.0Hz), 12.08(1H, s).

MS: 390(M+H)$^+$

Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 2 of Production Example 10.

mp. 165-167°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.12(3H, s), 2.79-3.09(8H, m), 6.75(1H, s), 7.16(4H, s), 8.14(2H, brs), 12.13(1H, brs).

MS: 290(M+H)$^+$ free

Production Example 110: Synthesis of N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride

Step 1

N-(4-{2-[4-(2-Aminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (7 mg), N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (6.57 mg), N,N-diisopropylethylamine (0.00748 ml), THF (0.5 ml) and DMF (0.1 ml) were combined under N_2 atmosphere. The reaction mixture was stirred at r.t. for 43 hours, and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with *n*-hexane / AcOEt (1:1) as an eluent to give di-tert-butyl ((Z)-{[2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl]amino}-methylidene)biscarbamate (5.9 mg) as colorless oil.

^{1}H-NMR [CD_3Cl/CD_3OD (1:1)], δ (ppm): 1.50(18H, s), 2.24(3H, s), 2.86(2H, t, J=7.0Hz), 2.95(4H, s), 3.62(2H, t, J=7.0Hz), 4.24(2H, s), 6.50(1H, s), 7.11(2H, d, J=8.5Hz), 7.16(2H, d, J=8.5Hz).

MS: 532(M+H)+

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR [CD_3Cl/CD_3OD (1:1)], δ (ppm): 2.41(3H, s), 2.87(2H, t, J=7.0Hz), 3.05(4H, s), 3.44(2H, t, J=7.0Hz), 6.86(1H, s), 7.18(4H, s).

MS: 332$(M+H)^+$ free

Production Example 111: Synthesis of N-{4-{4-[(2-{[amino(imino)methyl]amino}ethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

1-[4-(Methylthio)phenyl]ethanone (5.5 g) was dissolved in AcOH (55 ml), and then 90 % pyridinium tribromide (11.8 g) and 30 % hydrobromic acid in AcOH (5.5 ml) were added to the solution at 0°C. The reaction mixture was stirred at r.t. for 30 minutes, and poured into water. The mixture was extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid (8.03 g), thiourea (3.78 g) and EtOH (55 ml) were combined. The reaction mixture was refluxed for 1.5 hours under N_2 atmosphere. After cooled to r.t., the precipitate was filtered *in vacuo*. The solid was washed with EtOH and water to give 4-[4-(methylthio)phenyl]-1,3-thiazol-2-amine (7.48 g) as a pale yellow solid.

mp. 245-246°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.51(3H, s), 7.18(1H, s), 7.35(2H, d, J=8.5Hz), 7.67(2H, d, J=8.5Hz).

MS: 223$(M+H)^+$

Step 2

N-{4-[4-(Methylthio)phenyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 1 in a similar manner

according to Step 3 of Production Example 45.

mp. 235-236°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.50(3H, s), 7.31(2H, d, J=8.5Hz), 7.56(1H, s), 7.83(2H, d, J=8.5Hz), 12.24(1H, brs).

MS: 265$(M+H)^+$

Step 3

N-{4-[4-(Methylthio)phenyl]-1,3-thiazol-2-yl}acetamide (2 g) was suspended in CH_2Cl_2 (20 ml), and then 3-chloroperoxybenzoic acid (1.44 g) was added portionwise to the suspension at 0°C. The reaction mixture was stirred at r.t. for 15 minutes. The precipitate was filtered *in vacuo*, and the solid was washed with 1N-Na_2CO_3, water and EtOH to give N-{4-[4-(methylsulfinyl)phenyl]-1,3-thiazol-2-yl}acetamide (2.80 g) as a colorless solid.

mp. 274-274.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3H, s), 2.77(3H, s), 7.62(1H, s), 7.71(2H, d, J=8.5Hz), 8.07(2H, d, J=8.5Hz).

MS: 279$(M-H)^+$

Step 4

N-{4-[4-(Methylsulfinyl)phenyl]-1,3-thiazol-2-yl}acetamide (1.5 g), sodium acetate (1.54 g), and acetic anhydride (30 ml) were combined under N_2 atmosphere. The reaction mixture was refluxed for 2 hours. After cooled to r.t., the mixture was diluted in AcOEt. The organic solution was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid was washed with ethyl ether / *n*-hexane to give ({4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}thio)methyl acetate (811.2 mg) as an off-white solid.

mp. 144-145°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.07(3H, s), 2.17(3H, s), 5.53(2H, s), 7.50(2H, d, J=8.5Hz), 7.63(1H, s), 7.88(2H, d, J=8.5Hz),

12.27(1H, brs).

MS: 323(M+H)$^+$

Step 5

({4-[2-(Acetylamino)-1,3-thiazol-4-yl]phenyl}thio)methyl acetate (40 mg) was dissolved in CH_2Cl_2 (0.6 ml) and MeOH (0.3 ml) under N_2 atmosphere. Then magnesium monoperoxyphthalate (120 mg) was added to the solution at 0°C. The reaction mixture was stirred at r.t. for 2 hours. Water and $CHCl_3$ were added to the mixture, and the mixture was extracted. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give ({4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}sulfonyl)methyl acetate (29.7 mg) as a colorless solid.

mp. 237-238°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.07(3H, s), 2.18(3H, s), 5.43(2H, s), 7.94(1H, s), 7.97(2H, d, J=8.5Hz), 8.17(2H, d, J=8.5Hz), 12.37(1H, brs).

MS: 355(M+H)$^+$

Step 6

({4-[2-(Acetylamino)-1,3-thiazol-4-yl]phenyl}sulfonyl)methyl acetate (700 mg), THF (8 ml), MeOH (4 ml) and 1N-NaOH (1.98 ml) were combined. The reaction mixture was stirred at r.t. for 1.5 hours, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give sodium 4-[2-(acetylamino)-1,3-thiazol-4-yl]phenylsulfinate (731 mg) as a colorless solid.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 7.52(2H, d, J=8.0Hz), 7.54(1H, s), 7.84(2H, d, J=8.0Hz).

MS: 281(M-H)$^+$ free

Step 7

Sodium 4-[2-(acetylamino)-1,3-thiazol-4-yl]phenylsulfinate (600 mg) was dissolved in DMF (2 ml) under

N_2 atmosphere. Then 2-bromoethanol (0.168 ml) was added to the solution at 0°C. The reaction mixture was stirred at 100°C for 7 hours. After cooled to r.t., water and AcOEt were added to the mixture. The precipitate was filtered *in vacuo* to give N-{4-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl}acetamide (80.2 mg) as an off-white solid.

mp. 258-260°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 3.47(2H, t, J=6.0Hz), 3.70(2H, q, J=6.0Hz), 4.89(1H, t, J=6.0Hz), 7.89(1H, s), 7.94(2H, d, J=8.5Hz), 8.13(2H, d, J=8.5Hz), 12.36(1H, brs).

MS: 325(M-H)$^+$

Step 8

N-(4-{4-[(2-Hydroxyethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl)acetamide (200 mg), Et_3N (0.102 ml) and CH_2Cl_2 (4 ml) were combined under N_2 atmosphere, and then MsCl (0.05 ml) was added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 2 hours. MeOH/$CHCl_3$ and water were added to the mixture, and the mixture was extracted. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual solid (221.6 mg) was suspended in CH_3CN (10 ml), and then 28 % ammonia solution (0.5 ml) was added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 15 hours, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with [MeOH/$CHCl_3$ (1:30), then NH_4OH/MeOH/$CHCl_3$ (1:10:60)] as an eluent, and triturated with EtOH / ethyl ether to give N-(4-{4-[(2-aminoethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl)acetamide (60.4 mg) as an off-white solid.

mp. 287-288°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 2.79(2H, t, J=6.5Hz), 3.36(2H, q, J=6.5Hz), 7.90(1H, s), 7.94(2H, d, J=8.5Hz), 8.15(2H, d, J=8.5Hz).

MS: 326(M+H)$^+$

Step 9

Di-tert-butyl ((Z)-{[2-({4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}sulfonyl)ethyl]amino}methylidene)biscarbamate was prepared from the compound of Step 8 in a similar manner according to Step 3 of Production Example 31.

mp. 280-281°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.38(9H, s), 1.39(9H, s), 2.18(3H, s), 3.65(4H, s), 7.88(1H, s), 7.93(2H, d, J=8.5Hz), 8.13(2H, d, J=8.5Hz), 8.32(1H, brs), 11.32(1H, brs), 12.35(1H, brs).

MS: 568(M+H)$^+$

Step 10

The title compound was prepared from the compound of Step 9 in a similar manner according to Step 4 of Production Example 31.

mp. 188-189.5°C

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.18(3H, s), 3.51(2H, m), 3.59(2H, t, J=6.0Hz), 7.28(3H, brs), 7.62(1H, t, J=5.5Hz), 7.93(1H, s), 7.98(2H, d, J=8.5Hz), 8.17(2H, d, J=8.5Hz), 12.37(1H, brs).

MS: 368(M+H)$^+$ free

Production Example 112: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[3-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

N-Methoxy-N-methyl-3-(methylsulfonyl)benzamide was prepared from 3-(methylsulfonyl)benzoic acid in a similar manner according to Step 1 of Production Example 31.

^{1}H-NMR ($CDCl_3$), δ (ppm): 3.08(3H, s), 3.40(3H, s), 3.55(3H, s), 7.64(1H, t, J=8.0Hz), 7.99(1H, dt, J=8.0, 1.5Hz), 8.03(1H, dt, J=8.0, 1.5Hz), 8.28(1H, t, J=1.5Hz).

MS: 244(M+H)$^+$

Step 2

To a stirred solution of N-methoxy-N-methyl-3-

(methylsulfonyl)benzamide (5 g) in dry THF (100 ml) was added dropwise DIBALH (22.6 ml) at -78°C under N_2 atmosphere. The reaction mixture was stirred for 4 hours at r.t. and then quenched with MeOH at 0°C. AcOEt and 1N-HCl were added to the mixture, and extracted. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual oil (3.38 g), methyl (triphenylphosphoranylidene)acetate (6.87 g) and THF (68 ml) were combined at r.t. under N_2 atmosphere, and the reaction mixture was refluxed for 3 hours. The solvent was removed *in vacuo*, and the residue was suspended in AcOEt. The solid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / AcOEt (2:1) as an eluent to give methyl (2E)-3-[3-(methylsulfonyl)phenyl]acrylate (613.8 mg) as yellow oil.

^{1}H-NMR (DMSO-d_6), δ (ppm): 3.28(3H, s), 3.75(3H, s), 6.85(1H, d, J=16.0Hz), 7.74(1H, s), 7.93(1H, t, J=8.0Hz), 7.96(1H, d, J=8.0Hz), 8.09(1H, d, J=8.0Hz), 8.32(1H, d, J=16.0Hz).

Step 3

Methyl (2E)-3-[3-(methylsulfonyl)phenyl]acrylate (600 mg), MeOH (6 ml) and then 10 % palladium carbon (99.9 mg) were combined under N_2 atmosphere. The reaction mixture was stirred at r.t. for 7 hours under H_2 atmosphere (1 atm), and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with *n*-hexane / AcOEt (1:1 → 1:2) as an eluent to give methyl 3-[3-(methylsulfonyl)phenyl]propanoate (283.3 mg) as colorless oil.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.70(2H, t, J=7.5Hz), 2.97(2H, t, J=7.5Hz), 3.20(3H, s), 3.58(3H, s), 7.52-7.63(2H, m), 7.73-7.80(2H, m).

Step 4

Ethyl 4-[3-(methylsulfonyl)phenyl]-2-oxobutanoate was prepared from the compound of Step 3 in a similar manner according to Step 2 of Production Example 47.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.35(3H, t, J=7.0Hz), 3.05(2H, t, J=7.0Hz), 3.06(3H, s), 3.24(2H, t, J=7.0Hz), 4.32(2H, q, J=7.0Hz), 7.45-7.82(4H, m).

Step 5

Ethyl 3-bromo-4-[3-(methylsulfonyl)phenyl]-2-oxobutanoate was prepared from the compound of Step 4 in a similar manner according to Step 1 of Production Example 46.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.37(3H, t, J=7.0Hz), 3.07(3H, s), 3.34(1H, dd, J=14.5, 8.0Hz), 3.60(1H, dd, J=14.5, 6.5Hz), 4.35(2H, q, J=7.0Hz), 5.26(1H, dd, J=8.0, 6.5Hz), 7.49-7.88(4H, m).

Step 6

Ethyl 2-amino-5-[3-(methylsulfonyl)benzyl]-1,3-thiazole-4-carboxylate was prepared from the compound of Step 5 in a similar manner according to Step 2 of Production Example 46.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.24(3H, t, J=7.0Hz), 3.20(3H, s), 4.20(2H, q, J=7.0Hz), 4.46(2H, s), 7.10(2H, s), 7.57-7.61(2H, m), 7.76-7.83(2H, m).

MS: 341$(M+H)^+$

Step 7

Ethyl 2-(acetylamino)-5-[3-(methylsulfonyl)benzyl]-1,3-thiazole-4-carboxylate was prepared from the compound of Step 6 in a similar manner according to Step 3 of Production Example 45.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.27(3H, t, J=7.0Hz), 2.10(3H, s), 3.20(3H, s), 4.27(2H, q, J=7.0Hz), 4.61(2H, s), 7.56-7.66(2H, m), 7.77-7.89(2H, m), 12.47(1H, s).

MS: 383$(M+H)^+$

Step 8

Ethyl 2-(acetylamino)-5-[3-(methylsulfonyl)benzyl]-1,3-

thiazole-4-carboxylate (54.7 mg) was suspended in THF (1 ml) under N_2 atmosphere, and then lithium aluminium hydride (7.79 mg) was added portionwise to the suspension at 0°C. The reaction mixture was refluxed for 2.5 hours, and quenched with MeOH and 1N-HCl at 0°C. Anhydrous $MgSO_4$ was added to the mixture, and stirred at r.t. for 1 hour. The suspension was filtered *in vacuo*. The filtrate was concentrated *in vacuo*. The residual oil (114.8 mg), $CHCl_3$ (1 ml), CH_3CN (1 ml) and Dess-Martin periodinane (88 mg) were combined at 0°C under N_2 atmosphere. The reaction mixture was stirred at r.t. for 1 hour, and diluted in $CHCl_3$. The organic solution was washed with saturated $NaHCO_3$, water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give N-{4-formyl-5-[3-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (61.2mg) as a yellow amorphous.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.13(3H, s), 3.17(3H, s), 4.67(2H, s), 7.56-7.90(4H, m), 10.04(1H, s), 12.39(1H, s).

Step 9

N-{5-[3-(Methylsulfonyl)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 8 in a similar manner according to Step 5 of Production Example 45.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.08(3Hx2/3, s), 2.13(3Hx1/3, s), 3.18(3H, s), 4.23(2H×2/3, s), 4.50(2Hx1/3, s), 6.69-8.31(10H, m).

Step 10

N-{4-[2-(4-Aminophenyl)ethyl]-5-[3-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 9 in a similar manner according to Step 6 of Production Example 45.

MS: 430$(M+H)^+$

Step 11

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[3-

(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound of Step 10 in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR [CD_3Cl/CD_3OD (1:1)], δ (ppm): 1.29(9H, s), 1.55(9H, s), 2.23(3H, s), 2.89(4H, m), 3.07(3H, s), 3.90(2H, s), 7.11-7.87(8H, m).

MS: 672$(M+H)^+$

Step 12

The title compound was prepared from the compound of Step 11 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (CD_3OD), δ (ppm): 2.08(3H, s), 2.98(4H, m), 3.10(3H, s), 3.98(2H, s), 7.10-7.88(8H, m).

MS: 472$(M+H)^+$ free

Production Example 113: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1,3-thiazol-2-yl}acetamide dihydrochloride

Step 1

N-{5-[(1,1-Dioxido-4-thiomorpholinyl)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

MS: 437.12$(M+H)^+$

Step 2

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.23(3H, s),

2.70-2.95(8H, m), 2.95-3.12(4H, s), 3.45(2H, s), 6.99(2H, d, J=8.3Hz), 7.42(2H, d, J=8.3Hz), 8.94-9.24(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 651.1 $(M+H)^+$, 673.3 $(M+Na)^+$

Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 2.97(4H, s), 3.77-4.63(8H, s), 4.45(2H, s), 7.15(2H, d, J=8.3Hz), 7.32(2H, d, J=8.3Hz), 7.46(4H, s), 9.96(1H, s), 12.29(1H, s).

MS: 451.3 $(M+H)^+$, 473.2 $(M+Na)^+$

Production Example 114: Synthesis of N-[4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-(4-morpholinylmethyl)-1,3-thiazol-2-yl]acetamide dihydrochloride

Step 1

N-{5-(4-Morpholinylmethyl)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

MS: 389.16 $(M+H)^+$

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(4-morpholinylmethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.22(3H, s), 2.30-2.46(4H, m), 2.85(4H, s), 3.39(2H, s), 3.58-3.75(4H, m), 7.07(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz), 8.80-9.31(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 603.3 $(M+H)^+$

Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR(DMSO-d_6), δ (ppm): 2.16(3H, s), 2.97(4H, s), 3.00-3.12(2H, m), 3.16-3.27(2H, m), 3.65-3.76(2H, m), 3.86-3.97(2H, m), 4.43(2H, s), 7.15(2H, d, J=8.4Hz), 7.31(2H, d, J=8.4Hz), 7.40(4H, s), 9.86(1H, s), 10.54-10.84(1H, brs), 12.34(1H, s).
MS: 403.1$(M+H)^+$, 426.1$(M+Na)^+$

Production Example 115: Synthesis of N-{4-[2-({[amino(imino)methyl]amino}phenyl)ethyl]-5-[(3-oxo-1-piperazinyl)methyl]-1,3-thiazol-2-yl}acetamide dihydrochloride

Step 1

N-{4-[(Z)-2-(4-Nitrophenyl)vinyl]-5-[(3-oxo-1-piperazinyl)methyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

Z : E = 3 : 1

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3Hx3/4, s), 2.15(3Hx1/4, s), 2.54-2.59(2Hx3/4, m), 2.61-2.67(2Hx1/4, m), 2.93(2Hx3/4, s), 3.02(2Hx1/4, m), 3.08-3.19(2H, m), 3.64(2Hx3/4, s), 3.95(2Hx1/4, s), 6.72(1Hx3/4, d, J=12.4Hz), 6.78(1Hx3/4, d, J=12.4Hz), 7.34(1Hx1/4, d, J=15.7Hz), 7.59(1x1/4, d, J=15.7Hz), 7.62(2Hx3/4, d, J=8.8Hz), 7.76(1Hx3/4, s), 7.78(1Hx1/4, s), 7.90(2Hx1/4, d, J=8.8Hz), 8.14(2Hx3/4, d, J=8.8Hz), 8.21(2Hx1/4, d, J=8.8Hz), 11.75-12.06(1Hx3/4, brs), 12.08-12.33(1Hx1/4, brs).
MS: 402.21$(M+H)^+$

Step 2

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(3-oxo-1-piperazinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared

from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.24(3H, s), 2.47-2.55(2H, m), 2.80-2.93(4H, m), 3.13(2H, s), 3.24-3.32(2H, m), 3.43(2H, s), 6.02(1H, s), 7.04(2H, d, J=8.4Hz), 7.44(2H, d, J=8.3Hz), 9.02-9.26(1H, brs), 10.24(1H, s), 11.62(1H, s).

MS: 616.2$(M+H)^+$, 638.2$(M+Na)^+$

Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.15(3H, s), 2.39-2.62(2H, m), 2.95(4H, s), 3.08-3.86(4H, m), 4.20-4.77(2H, brs), 7.15(2H, d, J=8.3Hz), 7.30(2H, d, J=8.0Hz), 7.35(4H, s), 8.04-8.62(1H, brs), 9.70(1H, s), 10.67-11.38(1H, brs), 11.97-12.72(1H, brs).

MS: 416.2$(M+H)^+$ free

Production Example 116: Synthesis of 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N,N-dimethyl-1-piperazinecarboxamide dihydrochloride

Step 1

9H-Fluoren-9-ylmethyl 4-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl}methyl)-1-piperazinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.10(3H, s), 2.26-2.61(4H, m), 3.39-3.64(6H, m), 4.19-4.30(1H, m), 4.37-4.49(2H, m), 6.66(2H, s), 7.07-7.67(8H, m), 7.76(2H, d, J=6.9Hz), 8.05(2H, d, J=8.9Hz), 10.03(1H, s).

MS: 610.2$(M+H)^+$, 632.2$(M+Na)^+$

Step 2

9H-Fluoren-9-ylmethyl 4-({2-(acetylamino)-4-[2-(4-

aminophenyl)ethyl]-1,3-thiazol-5-yl}methyl)-1-piperazinecarboxylate was prepared from the compound of Step 1 in a similar manner according to Step 6 of Production Example 45.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.16-2.33(7H, m), 2.80(4H, s), 3.34(2H, s), 3.36-3.84(6H, m), 4.17-4.30(1H, m), 4.36-4.47(2H, m), 6.57(2H, d, J=8.4Hz), 6.86(2H, d, J=8.3Hz), 7.26-7.46(4H, m), 7.56(2H, d, J=7.0Hz), 7.76(2H, d, J=6.9Hz), 8.60-9.52(1H, brs).

MS: 582.2 $(M+H)^+$, 604.3 $(M+Na)^+$

Step 3

9H-Fluoren-9-ylmethyl 4-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-1-piperazinecarboxylate was prepared from the compound of Step 2 in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.52(9H, s), 2.23(3H, s), 2.28-2.43(4H, m), 2.86(4H, s), 3.36-3.55(6H, m), 4.18-4.29(1H, m), 4.35-4.48(2H, m), 7.05(2H, d, J=8.5Hz), 7.13-7.66(8H, m), 7.75(2H, d, J=7.0Hz), 8.85-9.76(1H, brs), 10.25(1H, Ss), 11.63(1H, s).

MS: 824.2 $(M+H)^+$, 847.3 $(M+Na)^+$

Step 4

To a solution of 9H-fluoren-9-ylmethyl 4-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-1-piperazinecarboxylate (400 mg) in DMF (0.8 ml) was added piperidine (0.16 ml), and the mixture was stirred for 2 h at 20°C. To the reaction mixture was added piperidine (0.16 ml), stirred at 20°C for 1 h and 40°C for 1 h, then cooled to 20°C, added AcOEt (50 ml), and the mixture was

washed with water (10 mlx3) and brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude pale yellow oil (463 mg). The crude oil was purified by flash column chromatography over NH silica gel with dichloromethane / methanol (100:0) → (100 : 1) as an eluent to give di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(1-piperazinylmethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate as a colorless amorphous.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.21(3H, s), 2.27-2.47(4H, m), 2.71-3.00(8H, m), 3.40(2H, s), 7.07(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz), 10.24(1H, s), 11.47-11.74(1H, brs).

MS: 602.3(M+H)$^+$, 624.2(M+Na)$^+$

Step 5

To a solution of di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(1-piperazinylmethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (30 mg) in dichloromethane (0.3 ml) were added N,N-diisopropylethylamine (9.55 μl) and dimethylcarbamyl chloride (4.59 μl), and the mixture was stirred for 14 h at 20°C. To the reaction mixture was added saturated sodium hydrogen carbonate aqueous solution (2 ml), then the mixture was extracted with diclhloromethane (5 mlx3) and the extract was dried over diatomaceous earth. The organic layer was concentrated *in vacuo* to give crude oil. The residue was purified by preparative silica gel thin-layer chromatography with chloroform / methanol (20:1) as an eluent to give di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(dimethylamino)carbonyl]-1-piperazinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate as colorless oil.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.54(9H, s), 2.23(3H, s), 2.35-2.42(4H, m), 2.80(6H, s), 2.81-2.89(4H, m), 3.17-3.27(4H, m), 3.41(2H, s), 7.07(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz),

8.73-8.90(1H, brs), 10.25(1H, s), 11.63(1H, s).

MS: 673.3(M+H)$^+$, 695.2(M+Na)$^+$

Step 6

The title compound was prepared from the compound of Step 5 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR(DMSO-d_6), δ (ppm): 2.16(3H, s), 2.76(6H, s), 2.91-3.06(6H, m), 3.07-3.19(2H, m), 3.20-3.30(2H, m), 3.57-3.65(2H, m), 4.36-4.51(2H, m), 7.15(2H, d, J=8.4Hz), 7.31(2H, d, J=8.4Hz), 7.41(4H, s), 9.87(1H, s), 10.51-10.69(1H, brs), 12.33(1H, s).

MS: 473.2(M+H)$^+$

Production Example 117: Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-(4-morpholinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-2-yl)acetamide dihydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(4-morpholinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 4 of Production Example 116 in a similar manner according to Step 5 of Production Example 116.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.54(9H, s), 2.23(3H, s), 2.32-2.46(4H, m), 2.78-2.91(4H, m), 3.20-3.30(8H, m), 3.42(2H, s), 3.63-3.71(4H, m), 7.07(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.72-8.89(1H, brs), 10.25(1H, s), 11.64(1H, s).

MS: 715.3(M+H)$^+$, 737.2(M+Na)$^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.90-3.07(6H, m), 3.11-3.32(8H, m), 3.48-3.76(6H, m), 4.42(2H, s), 7.15(2H, d,

J=8.4Hz), 7.31(2H, d, J=8.4Hz), 7.40(4H, s), 9.85(1H, s), 10.51-10.72(1H, brs), 12.34(1H, s).

MS: 515.3 $(M+H)^+$ free

Production Example 118: Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-(1-pyrrolidinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-2-yl)acetamide dihydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(1-pyrrolidinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 4 of Production Example 116 in a similar manner according to Step 5 of Production Example 116.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.54(9H, s), 1.72-1.89(4H, m), 2.23(3H, s), 2.28-2.48(4H, m), 2.84(4H, s), 3.19-3.39(8H, m), 3.41(2H, s), 7.07(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.71-8.99(1H, brs), 10.24(1H, s), 11.64(1H, s).

MS: 699.2 $(M+H)^+$, 721.3 $(M+Na)^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.70-1.83(4H, m), 2.16(3H, s), 2.89-3.05(6H, m), 3.06-3.19(2H, m), 3.20-3.32(6H, m), 3.64-3.84(2H, m), 4.36-4.50(2H, m), 7.15(2H, d, J=8.2Hz), 7.31(2H, d, J=8.3Hz), 7.42(4H, s), 9.88(1H, s), 10.50-10.75(1H, brs), 12.34(1H, s).

MS: 499.3 $(M+H)^+$ free

Production Example 119: Synthesis of N-[4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-({4-[(4-methyl-1-piperazinyl)carbonyl]-1-piperazinyl}methyl)-1,3-thiazol-2-yl]acetamide trihydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(4-methyl-1-piperazinyl)carbonyl]-1-piperazinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 4 of Production Example 116 in a similar manner according to Step 5 of Production Example 116.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.54(9H, s), 2.23(3H, s), 2.29(3H, s), 2.32-2.48(8H, m), 2.84(4H, s), 3.16-3.35(8H, m), 3.42(2H, s), 7.07(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.69-9.04(1H, brs), 10.24(1H, s), 11.64(1H, s).

MS: 728.2$(M+H)^+$, 750.3$(M+Na)^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.16(3H, s), 2.76(3H, d, J=4.6Hz), 2.89-3.09(8H, m), 3.17-3.39(8H, m), 3.62-3.77(4H, m), 4.34-4.51(2H, brs), 7.15(2H, d, J=8.3Hz), 7.31(2H, d, J=8.2Hz), 7.41(4H, s), 9.87(1H, s), 10.68-10.97(1H, brs), 12.34(1H, s).

MS: 528.3$(M+H)^+$ free

Production Example 120: Synthesis of 3-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}-N,N-dimethylpropanamide hydrochloride

Step 1

Ethyl 3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]acrylate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carbaldehyde in a similar manner according to Step 7 of Production Example 61.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.16-1.40(3H, m), 1.52(9H, s), 2.23-2.38(3H, m), 2.70-3.06(4H, m), 4.15-4.33(2H, m), 5.53-6.15(1H, m), 6.64-7.85(6H, m).

MS: 482.2 $(M+Na)^+$

Step 2

A mixture of ethyl (2E)-3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]acrylate and ethyl (2Z)-3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]acrylate (200 mg), THF (7 ml) and 10 % Pd/C (392 mg) were combined under nitrogen atmosphere. The mixture was stirred under 3 atm hydrogen atmosphere at 20°C for 3 h. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo* to give ethyl 3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]propanoate as a colorless amorphous.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.24(3H, t, J=7.0Hz), 1.51(9H, s), 2.24(3H, s), 2.41(2H, t, J=7.5Hz), 2.73-2.93(6H, m), 4.12(2H, q, J=7.0Hz), 6.95(2H, d, J=7.2Hz), 7.23(2H, d, J=7.7Hz).

MS: 484.1 $(M+Na)^+$

Step 3

Ethyl 3-(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)propanoate was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 65.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.24(3H, t, J=7.1Hz), 1.50(9H, s), 1.53(9H, s), 2.21(3H, s), 2.41(2H, t, J=7.6Hz), 2.70-3.00(6H, m), 4.12(2H, q, J=7.2Hz), 7.07(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.80-9.20(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 604.3 $(M+H)^+$, 626.2 $(M+Na)^+$

Step 4

3-(2-(Acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)propanoic acid was prepared from the compound of Step 3 in

a similar manner according to Step 1 of Production Example 42.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.47(9H, s), 1.53(9H, s), 2.19(3H, s), 2.25-2.45(2H, m), 2.60-3.00(6H, m), 6.96(2H, d, J=8.3Hz), 7.34(2H, d, J=8.3Hz), 10.17(1H, s), 11.30-11.90(1H, brs).

MS: 598.2$(M+Na)^+$

Step 5

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[3-(dimethylamino)-3-oxopropyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound of Step 4 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.21(3H, s), 2.28-2.43(2H, m), 2.79-2.99(12H, m), 7.05(2H, d, J=8.5Hz), 7.44(2H, d, J=8.5Hz), 8.85-9.37(1H, brs), 10.23(1H, s), 11.62(1H, s).

MS: 603.3$(M+H)^+$, 625.3$(M+Na)^+$

Step 6

The title compound was prepared from the compound of Step 5 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3H, s), 2.40(2H, t, J=7.3Hz), 2.75(2H, t, J=7.3Hz), 2.77-2.84(5H, m), 2.84-2.95(5H, m), 7.14(2H, d, J=8.4Hz), 7.24(2H, d, J=8.4Hz), 7.36(4H, s), 9.72(1H, s), 11.93(1H, s).

MS: 403.3$(M+H)^+$ free

Production Example 121: Synthesis of 3-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}-N-methylpropanamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[3-(methylamino)-3-oxopropyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound of Step 4 of Production Example 120 in a

similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.45(9H, s), 1.54(9H, s), 1.79-1.88(2H, s), 2.23(3H, s), 2.65(3H, d, J=4.8Hz), 2.69-2.77(2H, m), 2.79-2.86(2H, m), 2.86-2.95(2H, m), 6.04(2H, d, J=4.4Hz), 6.93(2H, d, J=8.4Hz), 7.28(2H, d, J=8.4Hz), 8.79-9.17(1H, brs), 10.28(1H, s), 11.60(1H, s).

MS: 589.3$(M+H)^+$, 611.3$(M+Na)^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3H, s), 2.22(2H, t, J=7.3Hz), 2.53(3H, d, J=4.8Hz), 2.72-2.82(4H, m), 2.82-2.90(2H, m), 7.15(2H, d, J=8.4Hz), 7.26(2H, d, J=8.4Hz), 7.38(4H, s), 7.79(1H, d, J=4.5Hz), 9.76(1H, s), 11.95(1H, s).

MS: 389.2$(M+H)^+$, 411.2$(M+Na)^+$ free

Production Example 122: Synthesis of 3-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}propanamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(3-amino-3-oxopropyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 4 of Production Example 120 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.47(9H, s), 1.53(9H, s), 1.57-1.67(2H, m), 2.24(3H, s), 2.65-2.76(2H, m), 2.76-2.87(2H, m), 2.87-2.99(2H, m), 5.37(1H, s), 6.14(1H, s), 6.90(2H, d, J=8.4Hz), 7.28(2H, d, J=8.4Hz), 8.88-9.28(1H, brs), 10.12(1H, s), 11.58(1H, s).

MS: 575.0$(M+H)^+$, 597.3$(M+Na)^+$

Step 2

The title compound was prepared from the compound of Step

1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.10(3H, s), 2.23(2H, t, J=7.3Hz), 2.71-2.83(4H, m), 2.83-2.91(2H, m), 6.81(1H, s), 7.14(2H, d, J=8.4Hz), 7.26(2H, d, J=8.4Hz), 7.31(1H, s), 7.35(4H, s), 9.70(1H, s), 11.94(1H, s).

MS: 375.2(M+H)$^+$, 397.0(M+Na)$^+$ free

Production Example 123: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N,N-dimethyl-4-piperidinecarboxamide dihydrochloride

Step 1

1-[(2-(Acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-4-piperidinecarboxylic acid was prepared from ethyl 1-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-4-piperidinecarboxylate in a similar manner according to Step 1 of Production Example 42.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.51(9H, s), 1.76-2.49(10H, m), 2.69-3.00(6H, m), 3.71(2H, s), 7.04(2H, d, J=8.5Hz), 7.42(2H, d, J=8.5Hz), 10.23(1H, s), 11.13-12.07(1H, brs).

MS: 645.3(M+H)$^+$, 667.2(M+Na)$^+$

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(dimethylamino)carbonyl]-1-piperidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 1 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.54(9H, s), 1.75-

1.89(2H, m), 1.92-2.03(2H, m), 2.22(3H, s), 2.37-2.49(1H, m), 2.80-2.95(9H, m), 3.02(3H, s), 3.43(2H, s), 7.08(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.61-9.19(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 672.2$(M+H)^+$, 694.3$(M+Na)^+$

Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.71-2.01(4H, m), 2.16(3H, s), 2.76-2.87(4H, m), 2.87-3.1(9H, m), 3.3-3.4(2H, m), 4.32-4.45(2H, m), 7.15(2H, d, J=4.2Hz), 7.31(2H, d, J=4.2Hz), 7.41(4H, s), 9.83-9.93(1H, m), 9.99-10.19(1H, m), 12.32-12.37(1H, m).

MS: 472.3$(M+H)^+$, 494.0$(M+Na)^+$ free

Production Example 124: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N-methyl-4-piperidinecarboxamide dihydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(methylamino)carbonyl]-1-piperidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 1 of Production Example 123 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.5(9H, s), 1.54(9H, s), 1.65-1.74(2H, m), 1.75-1.84(2H, m), 1.87-1.98(2H, m), 2-2.11(1H, m), 2.22(3H, s), 2.8(3H, d, J=4.8Hz), 2.82-2.91(6H, m), 3.39(2H, s), 5.5(1H, d, J=4.4Hz), 7.07(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz), 8.72-8.99(1H, brs), 10.23(1H, s), 11.62(1H, s).

MS: 658.3$(M+H)^+$, 680.3$(M+Na)^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.71-2.04(4H, m), 2.16(3H, s), 2.25-2.37(1H, m), 2.54-2.61(3H, m), 2.82-2.94(2H, m), 2.96(4H, s), 3.27-3.37(2H, m), 4.31-4.44(2H, m), 7.15(2H, d, J=8.4Hz), 7.30(2H, d, J=8.4Hz), 7.41(4H, s), 7.89-8.00(1H, m), 9.83-10.16(2H, m).

MS: 458.2(M+H)$^+$, 480.0(M+Na)$^+$ free

Production Example 125: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-4-piperidinecarboxamide dihydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(aminocarbonyl)-1-piperidinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 1 of Production Example 123 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.53(9H, s), 1.66-1.75(2H, m), 1.78-1.87(2H, m), 1.88-1.99(2H, m), 2.07-2.17(1H, m), 2.23(3H, s), 2.77-2.92(6H, m), 3.39(2H, s), 5.5(2H, s), 7.06(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz), 8.94-9.25(1H, brs), 10.23(1H, s), 11.61(1H, s).

MS: 644.2(M+H)$^+$, 666.3(M+Na)$^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.68-2.08(4H, m), 2.16(3H, s), 2.25-2.36(1H, m), 2.82-3.09(6H, m), 3.27-3.44(2H, m), 4.30-4.45(2H, m), 6.87-7.06(1H, m), 7.15(2H, d, J=8.4Hz), 7.30(2H, d, J=8.3Hz), 7.36-7.52(5H, m), 9.87-10.25(2H, m), 12.30-12.37(1H, m).

MS: 444.2(M+H)$^+$, 466.2(M+Na)$^+$ free

Production Example 126: Synthesis of (3R)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-

5-yl}methyl)-N,N-dimethyl-3-piperidinecarboxamide dihydrochloride

Step 1

Ethyl (3R)-1-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl}methyl)-3-piperidinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

MS: 459.20 $(M+H)^+$

Step 2

Ethyl (3R)-1-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.22(3H, t, J=7.2Hz), 1.31-1.78(21H, m), 1.79-2.06(2H, m), 2.07-2.18(1H, m), 2.22(3H, s), 2.43-2.62(1H, m), 2.62-2.75(1H, m), 2.84(4H, s), 2.88-3.01(1H, m), 3.42(2H, s), 4.11(2H, q, J=7.1Hz), 7.08(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.76-9.16(1H, brs), 10.24(1H, s), 11.64(1H, s).

MS: 673.3 $(M+H)^+$, 695.2 $(M+Na)^+$

Step 3

(3R)-1-[(2-(Acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylic acid was prepared from the compound of Step 2 in a similar manner according to Step 1 of Production Example 42.

MS: 645.37 $(M+H)^+$

Step 4

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(3R)-3-

[(dimethylamino)carbonyl]-1-piperidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 3 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.39-1.57(20H, m), 1.66-1.73(1H, m), 1.74-1.83(1H, m), 1.87-1.98(1H, m), 2.08-2.19(1H, m), 2.22(3H, s), 2.72-2.94(10H, m), 3.02(3H, s), 3.41(2H, s), 7.08(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.70-9.02(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 672.41$(M+H)^+$

Step 5

The title compound was prepared from the compound of Step 4 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.29-1.94(4H, m), 2.16(3H, s), 2.77-3.33(15H, m), 4.27-4.46(2H, m), 7.16(2H, d, J=8.3Hz), 7.27-7.35(2H, m), 7.36-7.48(4H, m), 9.8-9.98(1H, m), 10.22-10.51 (1H, brs), 12.29-12.36(1H, m).

MS: 472.3$(M+H)^+$, 494.2$(M+Na)^+$ free

Production Example 127: Synthesis of (3R)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N-methyl-3-piperidinecarboxamide dihydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(3R)-3-[(methylamino)carbonyl]-1-piperidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 3 of Production Example 126 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.50(9H, s), 1.52-1.72(12H, m), 1.84-1.98(1H, m), 2.01-2.14(1H, m), 2.14-2.23(1H, m), 2.24(3H, s), 2.43-2.51(1H, m), 2.64-2.76(1H, m), 2.76-2.94(8H, m), 3.32(1H, d, J=14Hz), 3.41(1H, d, J=14Hz), 7.06(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz), 7.53(1H, brs), 8.84(1H, brs), 10.24(1H,

s), 11.63(1H, s).

MS: 658.39$(M+H)^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.31-1.94(4H, m), 2.16(3H, s), 2.54-3.36(12H, m), 4.27-4.48(2H, m), 7.12-7.19(2H, m), 7.25-7.35(2H, m), 7.35(4H, brs), 8.05-8.37(1H, m), 9.79-9.92(1H, m), 10.16-10.42(1H, brs), 12.29-12.37(1H, m).

MS: 458.2$(M+H)^+$, 480.1$(M+Na)^+$ free

Production Example 128: Synthesis of (3S)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N,N-dimethyl-3-piperidinecarboxamide dihydrochloride

Step 1

Ethyl (3S)-1-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl}methyl)-3-piperidinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

MS: 459.21$(M+H)^+$

Step 2

Ethyl (3S)-1-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.22(3H, t, J=7.2Hz), 1.3-1.79(21H, m), 1.8-2.06(2H, m), 2.08-2.18(1H, m), 2.22(3H, s), 2.43-2.62(1H, m), 2.62-2.75(1H, m), 2.84(4H, s), 2.88-3.01(1H, m), 3.42(2H, s), 4.11(2H, q, J=7.1Hz), 7.08(2H, d, J=8.4Hz),

7.46(2H, d, J=8.4Hz), 8.71-9.23(1H, brs), 10.24(1H, s), 11.64(1H, s).

MS: 673.3 $(M+H)^+$, 695.2 $(M+Na)^+$

Step 3

(3S)-1-[(2-(Acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylic acid was prepared from the compound of Step 2 in a similar manner according to Step 1 of Production Example 42.

MS: 645.36 $(M+H)^+$

Step 4

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(3S)-3-[(dimethylamino)carbonyl]-1-piperidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 3 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.4-1.64(20H, m), 1.65-1.73(1H, m), 1.73-1.82(1H, m), 1.86-1.97(1H, m), 2.08-2.18(1H, m), 2.22(3H, s), 2.7-2.93(10H, m), 3.02(3H, s), 3.41(2H, s), 7.08(2H, d, J=8.4Hz), 7.46(2H, d, J=8.3Hz), 8.61-8.99(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 672.39 $(M+H)^+$

Step 5

The title compound was prepared from the compound of Step 4 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.29-1.93(4H, m), 2.16(3H, s), 2.77-3.35(15H, m), 4.27-4.45(2H, m), 7.16(2H, d, J=8.4Hz), 7.28-7.35(2H, m), 7.35-7.47(4H, m), 9.8-9.96(1H, m), 10.21-10.46(1H, brs), 12.29-12.36(1H, m).

MS: 472.3 $(M+H)^+$, 494.2 $(M+Na)^+$ free

Production Example 129: Synthesis of (3S)-1-({2-(acetylamino)-

4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N-methyl-3-piperidinecarboxamide dihydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(3S)-3-[(methylamino)carbonyl]-1-piperidinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 3 of Production Example 128 in a similar manner according to Step 1 of Production Example 32.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.46-1.72(21H, m), 1.84-1.97(1H, m), 1.99-2.14(1H, m), 2.15-2.22(1H, m), 2.24(3H, s), 2.43-2.51(1H, m), 2.65-2.76(1H, m), 2.76-2.91(8H, m), 3.32(1H, d, J=14Hz), 3.41(1H, d, J=14Hz), 7.06(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz), 7.54(1H, brs), 8.84-9.02(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 658.40$(M+H)^+$

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.31-1.94(4H, m), 2.16(3H, s), 2.53-3.36(12H, m), 4.24-4.46(2H, m), 7.12-7.19(2H, m), 7.25-7.35(2H, m), 7.36(4H, brs), 8.06-8.37(1H, m), 9.83-9.99(1H, m), 10.28-10.54(1H, brs), 12.33(1H, s).

MS: 458.2$(M+H)^+$, 480.2$(M+Na)^+$ free

Production Example 130: Synthesis of N-{4-[2-(2-amino-1H-benzimidazol-6-yl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

N-{4-[2-(3,4-Dinitrophenyl)vinyl]-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl}acetamide was prepared from 2-(acetylamino)-5-[4-(methylthio)benzyl]-1,3-thiazole-4-carbaldehyde in a similar manner according to Step 5 of Production Example 45.

Z : E = 3 : 1

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.08(3Hx3/4, s), 2.12(3Hx1/4, s), 2.44(3H, s), 4.13(2Hx3/4, s), 4.32(2Hx1/4, s), 6.71(1Hx3/4, d, J=12.5Hz), 6.97(1Hx3/4, d, J=12.3Hz), 7.06-8.61(7H + 2Hx1/4, m), 11.85(1Hx3/4, s), 12.18(1Hx1/4, s).

MS: 471.1 $(M+H)^+$, 493.9 $(M+Na)^+$

Step 2

N-{4-[2-(3,4-Diaminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 32 and Step 6 of Production Example 45.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.23(3H, s), 2.70-2.85(4H, m), 3.03(3H, s), 3.88(2H, s), 6.34(1H, d, J=1.8Hz), 6.39(1H, dd, J=1.8, 7.8Hz), 6.56(1H, d, J=7.7Hz), 7.14(2H, d, J=8.3Hz), 7.79(2H, d, J=8.4Hz), 8.30-9.45(1H, brs).

MS: 445.0 $(M+H)^+$, 467.0 $(M+Na)^+$

Step 3

To a suspension of N-{4-[2-(3,4-diaminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (70.8 mg) in MeOH (0.7 ml) was added cyanogen bromide (25.3 mg), then the mixture was stirred for 14 h at 20°C. To the reaction mixture was added 1N-NaOH (0.239 ml) and the mixture was concentrated *in vacuo*. To the residue was added $CHCl_3$: MeOH = 10 : 1 (10 ml), and an insoluble material was removed by filtration. The filtrate was purified by flash column chromatography over NH silica gel with $CHCl_3$ / MeOH (100:1 → 10:1) as an eluent to give colorless oil. The oil was solidified with CH_2Cl_2 : Et_2O = 2 : 1 to give N-{4-[2-(2-amino-1H-benzimidazol-6-yl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide as a white solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.09(3H, s), 2.85(4H, s), 3.16(3H, s), 3.97(2H, s), 6.01(2H, s), 6.55-6.77(1H, m), 6.78-6.90(1H, m),

6.96(1H, d, J=7.8Hz), 7.10-7.30(2H, brs), 7.72(2H, d, J=8.1Hz), 10.55(1H, d, J=10.5Hz), 11.50-12.20(1H, brs).

MS: 470.2(M+H)$^+$, 492.1(M+Na)$^+$

Production Example 131: Synthesis of N-{4-[2-(2-amino-1H-benzimidazol-6-yl)ethyl]-1,3-thiazol-2-yl}acetamide

Step 1

N-{4-[2-(3,4-Dinitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from 2-(acetylamino)-1,3-thiazole-4-carbaldehyde in a similar manner according to Step 5 of Production Example 1.

Z : E = 8 : 1

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.13(3Hx8/9, s), 2.17(3Hx1/9, s), 6.64(1Hx8/9, d, J=12.6Hz), 6.80(1Hx8/9, d, J=12.6Hz), 7.29(1Hx1/9, d, J=15.7Hz), 7.33(1Hx8/9, s), 7.39(1Hx1/9, s), 7.63(1Hx1/9, d, J=15.7Hz), 8.00-8.50(3H, m), 11.97(1Hx8/9, s), 12.30(1Hx1/9, s).

MS: 335.0(M+H)$^+$, 357.1(M+Na)$^+$

Step 2

N-{4-[2-(3,4-Diaminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 1 in a similar manner according to Step 6 of Production Example 1.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.22(3H, s), 2.58-3.17(8H, m), 6.46-6.56(3H, m), 6.62(1H, d, J=8.3Hz), 8.84-10.42(1H, brs).

MS: 277.1(M+H)$^+$, 299.2(M+Na)$^+$

Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 3 of Production Example 130.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.11(3H, s), 2.79-2.97(4H, m), 6(2H, s), 6.59-6.8(2H, m), 6.91(1H, s), 6.97(1H, d, J=7.9Hz), 10.34-10.73(1H, brs), 11.94-12.22(1H, brs).

MS: 302.2(M+H)$^+$, 324.1(M+Na)$^+$

Production Example 132: Synthesis of N-({2-(acetylamino)-4-[2-

(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N-methylacetamide hydrochloride

Step 1

N-{5-[(Methylamino)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.05(3H, s), 2.46(3H, s), 3.75(2H, s), 6.67(2H, s), 7.41(2H, d, J=8.9Hz), 8.01(2H, d, J=8.8Hz), 9.7-11.69(1H, brs).

MS: 333.1$(M+H)^+$, 355.1$(M+Na)^+$

Step 2

To a suspension of N-{5-[(methylamino)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (46.8 mg) in dichloromethane (0.5 ml) were added N,N-diisopropylethylamine (27 μl) and acethyl chloride (10 μl), and the mixture was stirred for 2 h at 20°C. To the reaction mixture were added dichloromethane (5 ml), N,N-diisopropylethylamine (27 μl) and acethyl chloride (10 μl), and the mixture was stirred for 5 min. at 20°C, then washed with saturated sodium hydrogen carbonate aqueous solution (5 ml) and brine (5 ml), dried over $MgSO_4$, filtered and evaporated to give a yellow solid (67.8 mg). The crude compound was purified by preparative silica gel thin-layer chromatography with chloroform / methanol (20:1) as an eluent to give N-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl}methyl)-N-methylacetamide as a yellow solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.12(3Hx2/3, s), 2.13(3Hx1/3, s), 2.14(3Hx2/3, s), 2.24(3Hx1/3, s), 3.02(3Hx2/3, s), 3.05(3Hx1/3, s), 4.62(2Hx2/3, s), 4.79(2Hx1/3, s), 6.61(1Hx1/3, d, J=12.6Hz), 6.70(1Hx2/3, d, J=12.6Hz), 6.77(1Hx1/3, d, J=12.6Hz), 6.82(1Hx2/3, d, J=12.6Hz),

7.43(2Hx2/3, d, J=8.8Hz), 7.65(2Hx1/3, d, J=8.8Hz), 8.06(2Hx2/3, d, J=8.8Hz), 8.22(2Hx1/3, d, J=8.8Hz), 9.09-9.26(1Hx1/3, brs), 9.26-9.51(1Hx2/3, brs).

MS: 375.2(M+H)$^+$, 397.1(M+Na)$^+$

Step 3

N-({2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-5-yl}methyl)-N-methylacetamide was prepared from the compound of Step 2 in a similar manner according to Step 6 of Production Example 45.

MS: 347.25(M+H)$^+$

Step 4

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[acetyl(methyl)amino]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 3 in a similar manner according to Step 3 of Production Example 31.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.06(3Hx3/4, s), 2.12(3Hx1/4, s), 2.23(3H, s), 2.77(3Hx1/4, s), 2.81(3Hx3/4, s), 2.90(4H, s), 4.20(2Hx1/4, s), 4.46(2Hx3/4, s), 7.01(2Hx1/4, d, J=8.6Hz), 7.07(2Hx3/4, d, J=8.5Hz), 7.43(2Hx3/4, d, J=8.5Hz), 7.46(2Hx1/4, d, J=8.0Hz), 8.81-9.09(1H, brs), 10.22(1Hx3/4, s), 10.25(1Hx1/4, s), 11.62(1H, s).

MS: 589.2(M+H)$^+$, 611.2(M+Na)$^+$

Step 5

The title compound was prepared from the compound of Step 4 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (DMSO-d_6), δ (ppm): 1.98(3Hx3/4, s), 2.02(3Hx1/4, s), 2.11(3Hx3/4, s), 2.12(3Hx1/4, s), 2.60(3Hx1/4, s), 2.82(3Hx3/4, s), 2.89(4H, s), 4.39(2Hx3/4, s), 4.45(2Hx1/4, s), 7.13(2Hx1/4, d, J=8.1Hz), 7.14(2Hx3/4, d, J=8.4Hz), 7.22(2Hx1/4, d, J=8.4Hz), 7.25(2Hx3/4, d, J=8.4Hz), 7.31(4H,

s), 9.61(1H, s), 12.03(1Hx3/4, s), 12.13(1Hx1/4, s).
MS: 389.19(M+H)$^+$ free

Production Example 133: Synthesis of N-[4-(2-{4-[(2-aminoethyl)amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide dihydrochloride

Step 1

To a suspension of N-{4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (100 mg) in toluene were added tert-butyl (2-bromoethyl)carbamate (87.5 mg) and N,N-diisopropylethylamine (52 μl), and the mixture was stirred at 80°C for 24 h. The reaction mixture was allowed to cool to room temperature, water (10 ml) was added, and the organic layer was separated, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give tert-butyl {2-[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]ethyl}carbamate as a pale brown amorphous.

^{1}H-NMR ($CDCl_3$), δ (ppm): 1.45(9H, s), 2.23(3H, s), 2.86(4H, s), 3.15-3.28(2H, m), 3.15-3.47(2H, m), 4.64-5.02(1H, brs), 6.49(1H, s), 6.52(2H, d, J=8.0Hz), 6.95(2H, d, J=8.0Hz), 9.22-10.10(1H, brs).
MS: 405.2(M+H)$^+$, 427.3(M+Na)$^+$

Step 2

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 2 of Production Example 10.

^{1}H-NMR (DMSO-d_6), δ (ppm): 2.11(3H, s), 2.81(4H, s), 2.92-3.05(2H, m), 3.29(2H, t, J=6.2Hz), 6.67(2H, d, J=7.7Hz), 7.01(2H, d, J=8.1Hz), 7.87-8.24(3H, brs), 12.08(1H, s).
MS: 305.2(M+H)$^+$, 327.2(M+Na)$^+$

Production Example 134: Synthesis of N-{4-[3-(2-{[amino(imino)methyl]amino}ethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

To a suspension of lithium aluminium hydride in dry tetrahydrofuran (50 ml) was added (3-bromophenyl)acetic acid (10 g) in tetrahydrofuran (100 ml) under ice cooling. The mixture was refluxed for 2 hours. After cooling, to the reaction mixture were added water and aqueous Rochelle salt. The mixture was stirred for another 30 min. Aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 2-(3-bromophenyl)ethanol. This compound was used for the next reaction without further purification.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.66(1H, brs), 2.84(2H, dd, J=6.5, 14Hz), 3.85(2H, dt, J=6.5, 2.6Hz), 7.13-7.39(4H, m).

Step 2

To a solution of 2-(3-bromophenyl)ethanol (7 g) in N,N-dimethylformamide (100 ml) were added tert-butyldimethylsilyl chloride (5.77 g) and imidazole (2.84 g) at 25°C. The mixture was stirred at 25°C for 12 h. The reaction mixture was poured into water (500 ml) and extracted with ethyl acetate (100 mlx2). The combined organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with mixed solvent of n-hexane and ethyl acetate to give [2-(3-bromophenyl)ethoxy](tert-butyl)dimethylsilane as colorless oil.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 0.01(6H, s), 0.88(9H, s), 2.81(2H, dt, J=6.5, 9.5Hz), 3.81(2H, dt, J=3.0, 6.5Hz), 7.14-7.39 (5H, brs).

Step 3

To a solution of 1.6 g of [2-(3-bromophenyl)ethoxy](tert-butyl)dimethylsilane in tetrahydrofuran (20 ml) was added n-BuLi in hexane (1.57M, 3.88 ml) at -70°C, then the reaction mixture was stirred at same temperature for 30 min. To the

solution was added dimethylacetamide (1.42 ml) drop wise at the same temperature. The mixture was stirred for another 1 hour. To the reaction mixture were added water and 8 ml of 1N HCl under ice-cooling. The mixture was stirred for 1 hour, then extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with n-hexane and ethyl acetate (20/1-10/1) as an eluent to give 1-[3-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)phenyl]ethanone (350 mg) as colorless oil.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 0.03(6H, s), 0.85(9H, s), 2.61(3H, s), 2.87(2H, t, J=6.7 Hz), 3.82(2H, t, J=6.7Hz), 7.20-7.24(1H, m), 7.35-7.44(2H, m), 7.77-7.82(2H, m).

MS: 279$(M+H)^+$

Step 4

To a solution of 1-[3-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)phenyl]ethanone (755 mg) in tetrahydrofuran (4 ml) was added bromine (168 ml) drop wise at 0°C. The mixture was stirred at 25°C for 1 h. To the reaction mixture was added aq. saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give crude of 2-bromo-1-[3-(2-hydroxyethyl)phenyl]ethanone as colorless oil. This compound was used for the next reaction without further purification.

Step 5

To a solution of 2-bromo-1-[3-(2-hydroxyethyl)phenyl]ethanone (crude, 658 mg) in tetrahydrofuran (15 ml) was added 1-acetyl-2-thiourea (320 mg) at 25°C. The mixture was stirred at 60°C for 2 h. The residual colorless crystals were collected by filtration. The crystals were washed with isopropyl ether, and dried under reduced

pressure to give N-{4-[3-(2-hydroxyethyl)phenyl]-1,3-thiazol-2-yl}acetamide (514 mg) as a colorless crystal.

^{1}H-NMR (200 MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.76(2H, t, J=6.9Hz), 3.63(2H, t, J=6.9 Hz), 4.89(1H, brs), 7.16(1H, d, J=7.7 Hz), 7.32(1H, dd, J=7.7, 7.6Hz), 7.56(1H, s), 7.70(2H, d, J=7.6 Hz), 7.76(1H, s), 12.24(1H, s).

MS: 263$(M+H)^+$

Step 6

To a suspension of N-{4-[3-(2-hydroxyethyl)phenyl]-1,3-thiazol-2-yl}acetamide (300 mg) in CH_2Cl_2 (10 ml) were added methansulfonyl chloride (106 μl) and triethylamine (207 μl) at 5°C. The mixture was stirred at 25°C for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Resulting residue was purified by silica gel column chromatography with n-hexane and ethyl acetate (1:1) as an eluent to give 2-{3-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl methanesulfonate (388 mg) as a colorless solid.

^{1}H-NMR (200 MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 3.04(2H, t, J=6.9 Hz), 3.12(3H, s), 4.45(2H, t, J=6.9 Hz), 7.23-7.42(2H, m), 7.60(1H, s), 7.75-7.81(2H, m), 12.26(1H, s).

MS: 341$(M+H)^+$

Step 7

To a solution of 2-{3-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl methanesulfonate (388 mg) in N,N-dimethylformamide (5 ml) were added di-tert-butyliminodicarboxylate (322 mg) and K_2CO_3 (236 mg) at 25°C. The mixture was stirred at 80°C for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure.

Resulting colorless oil containing N-{4-(3-[2-(di-(tert-butoxycarbonyl)amino}ethyl]phenyl)-1,3-thiazol-2-yl}acetamide was used for the next reaction without further purification.

Step 8

N-{4-[3-(2-Aminoethyl)phenyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 7 in a similar manner according to Step 2 of Production Example 31.

^{1}H-NMR (200 MHz, DMSO-d_6), δ (ppm): 2.16(1H, s), 2.74(2H, dd, J=6.8, 6.2Hz), 2.88(2H, dd, J=7, 7.8Hz), 7.17(1H, d, J=7.7Hz), 7.35(1H, dd, J=7.7, 8Hz), 7.58(1H, s), 7.73(1H, d, J=8Hz), 7.74(1H, s).

MS: 262 $(M+H)^+$

Step 9

Di-tert-butyl {(Z)-[(2-{3-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)amino]methylidene}biscarbamate was prepared from the compound of Step 8 in a similar manner according to Step 5 of Production Example 18.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.45(9H, s), 1.50(3H, s), 2.27(3H, s), 2.92(2H, t, J=7.5Hz), 3.71(2H, dt, J=7.5, 7.2Hz), 7.11-7.41(4H, d), 7.65-7.78(1H, m).

MS: 504 $(M+H)^+$

Step 10

The title compound was prepared from the compound of Step 9 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 2.16(3H, s), 2.83(2H, t, J=6.9Hz), 3.41(2H, m), 7.23(1H, d, J=7.7Hz), 7.38(1H, dd, J=7.7, 7.8 Hz), 7.52(1H, t, J=5.5Hz), 7.59(1H, s), 7.75(1H, d, J=8.1Hz), 7.79(1H, s), 12.23(1H, s).

MS: 304 $(M+H)^+$ free

Production Example 135: Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

hydrochloride

Step 1

tert-Butyl N-{4-[2-(2-(acetylamino)-5-{(E)-2-[4-(methylsulfonyl)phenyl]vinyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from 2-(acetylamino)-4-{2-[4-(tert-butoxycarbonylamino)phenyl]ethyl}-1,3-thiazole-5-carbaldehyde in a similar manner according to Step 5 of Production Example 45.

MS: 542 $(M+H)^+$ free

Step 2

tert-Butyl N-{4-[2-(2-(acetylamino)-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from the compound of Step 1 in a similar manner according to Step 6 of Production Example 45.

MS: 544 $(M+H)^+$

Step 3

N-(4-[2-(4-Aminophenyl)ethyl]-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide was prepared from the compound of Step 2 in a similar manner according to Step 2 of Production Example 31.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 2.23(3H, s), 2.61(4H, s), 2.78(4H, s), 2.98(3H, s), 3.55(2H, brs), 6.57(2H, d, J=8.5Hz), 6.81(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.82(2H, d, J=8.5Hz), 8.80(1H, s).

MS: 444 $(M+H)^+$

Step 4

Di-tert-butyl [(E)-({4-[2-(2-(acetylamino)-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 3 in a similar manner according to Step 5 of Production Example 18.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.49(9H, s), 1.53(9H, s),

2.22(3H, s), 2.59-2.73(4H, m), 2.84(4H, s), 2.98(3H, s), 6.99(2H, d, J=8.4Hz), 7.28(2H, d, J=8.4Hz), 7.44(2H, d, J=8.4Hz), 7.83(2H, d, J=8.4Hz), 8.99(1H, bra), 10.23(1H, s), 11.62(1H, s).

MS: $686(M+H)^+$

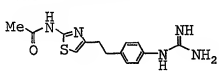
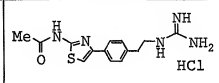
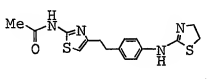
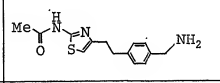
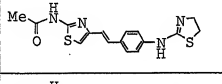
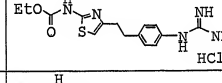
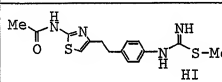
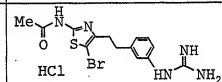
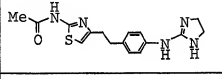
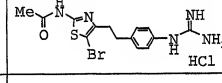
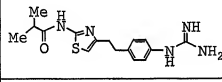
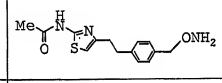
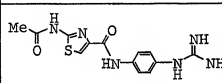
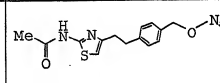
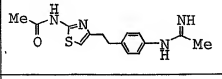
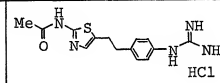
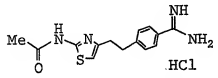
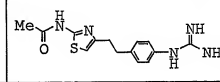
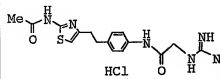
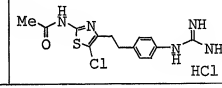
Step 5

The title compound was prepared from the compound of Step 4 in a similar manner according to Step 4 of Production Example 31.

^{1}H-NMR (200 MHz, DMSO-d_6), δ (ppm): 2.16(3H, s), 2.67(4H, brs), 2.82-2.94(4H, m), 3.14(3H, s), 7.12(2H, d, J=8.4Hz), 7.20(2H, d, J=8.4Hz), 7.43(2H, d, J=8.4Hz), 7.82(2H, d, J=8.4Hz), 9.87(1H, s), 11.97(1H, s).

MS: $486(M+H)^+$

The compounds according to the present invention useful as VAP-1 inhibitors are listed in the following tables.

No.	Structure	No.	Structure
1	 Compound A	11	 HCl
2		12	
3		13	 HCl
4	 HI	14	 HCl
5		15	 HCl
6		16	
7		17	
8		18	 HCl
9	 HCl	19	
10	 HCl	20	 HCl

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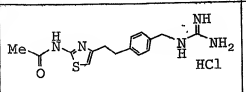
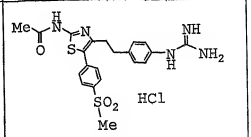
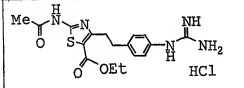
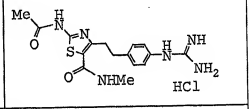
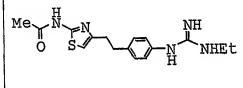
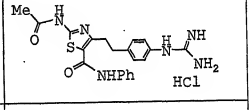
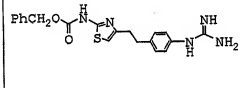
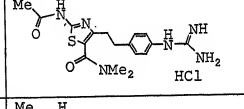
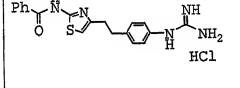
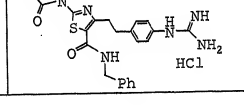
21		26	
22		27	
23		28	
24		29	
25		30	

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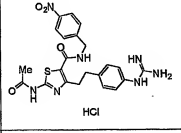
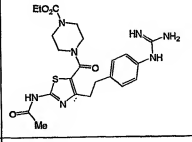
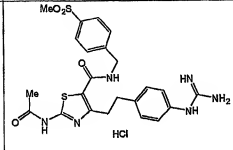
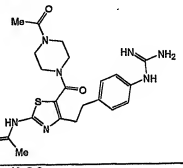
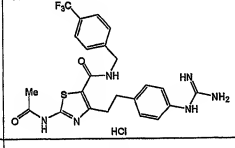
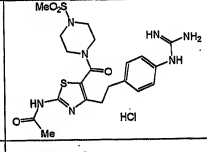
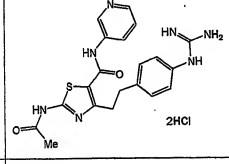
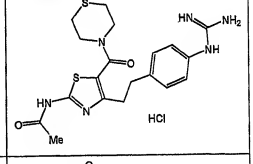
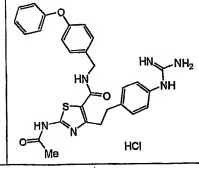
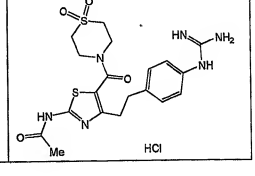
31	 HCl	36	
32	 HCl	37	
33	 HCl	38	 HCl
34	 2HCl	39	 HCl
35	 HCl	40	 HCl

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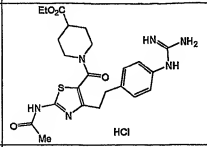
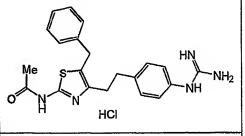
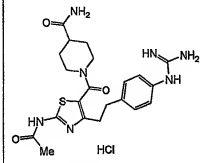
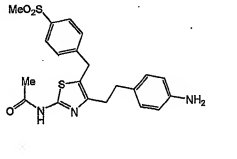
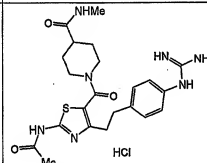
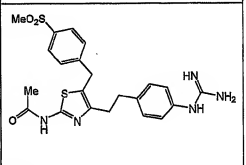
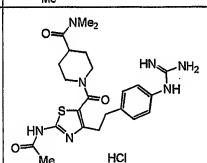
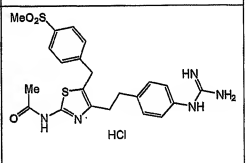
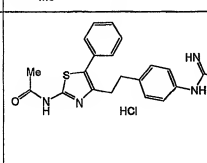
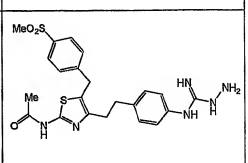
41		46	
42		47	
43		48	
44		49	
45		50	

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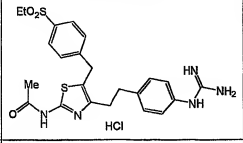
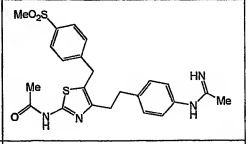
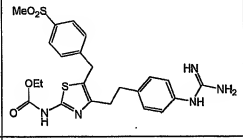
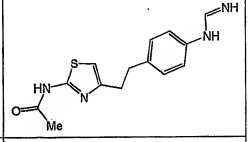
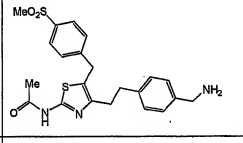
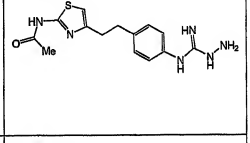
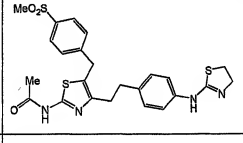
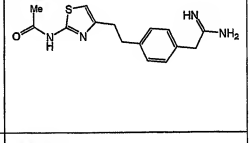
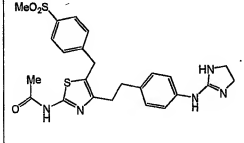
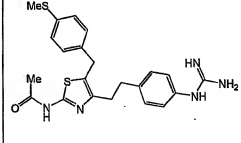
51		56	
52		57	
53		58	
54		59	
55		60	

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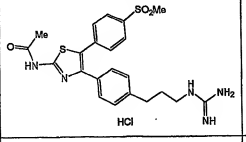
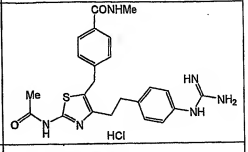
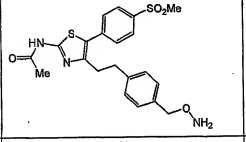
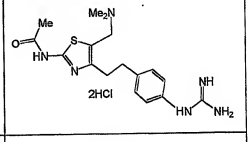
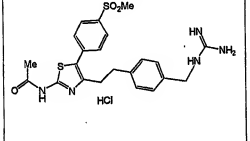
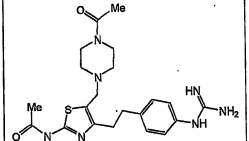
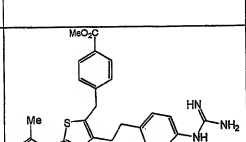
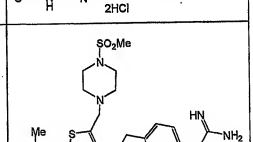
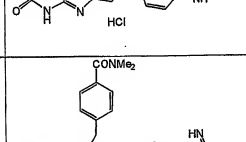
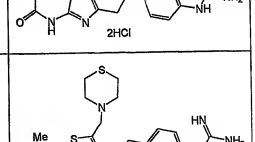
61		66	
62		67	
63		68	
64		69	
65		70	

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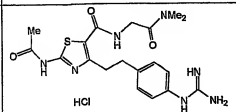
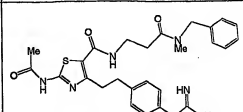
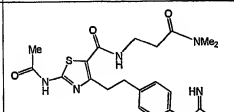
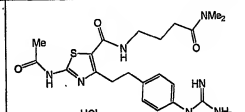
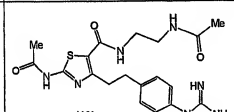
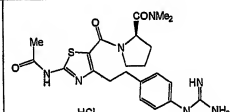
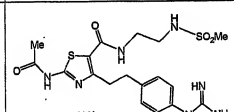
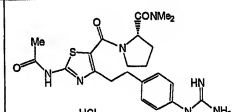
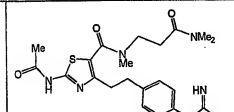
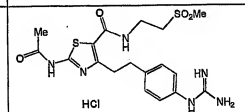
71		76	
72		77	
73		78	
74		79	
75		80	

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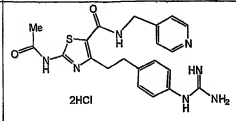
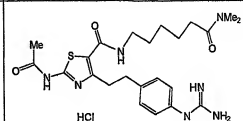
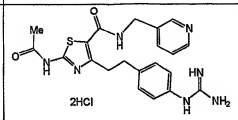
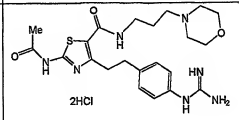
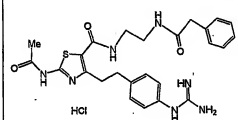
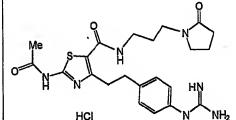
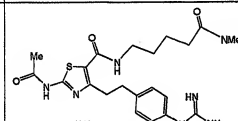
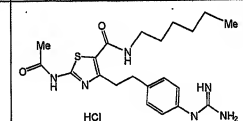
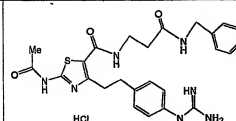
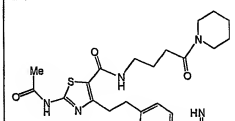
81		86	
82		87	
83		88	
84		89	
85		90	

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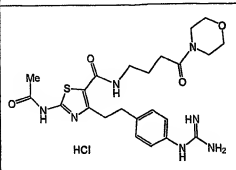
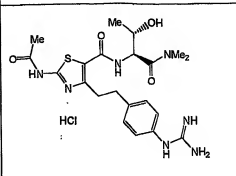
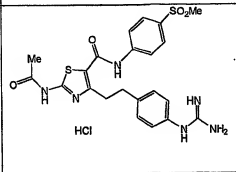
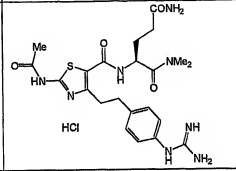
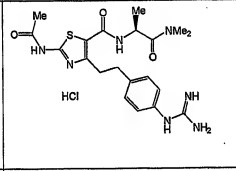
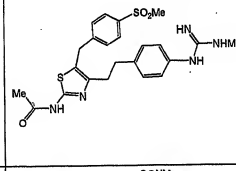
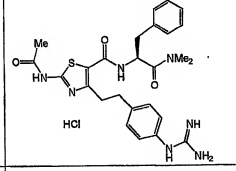
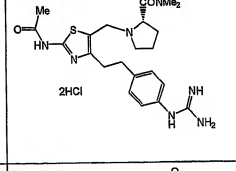
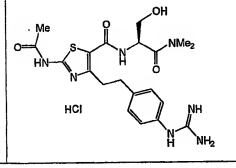
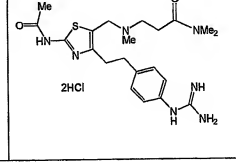
91		96	
92		97	
93		98	
94		99	
95		100	

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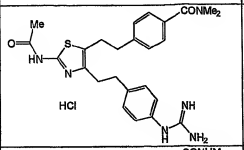
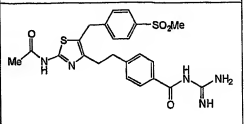
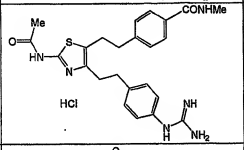
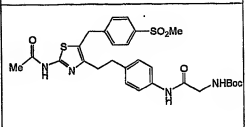
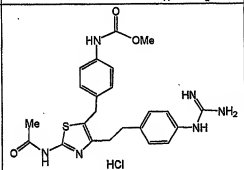
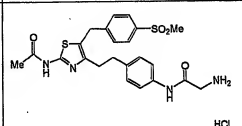
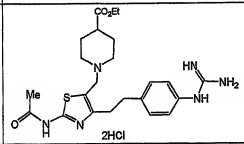
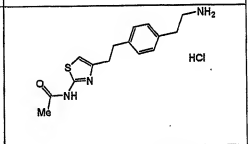
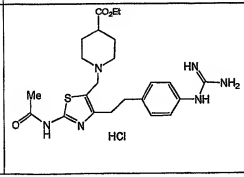
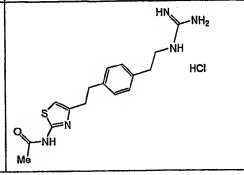
101		106	
102		107	
103		108	
104		109	
105		110	

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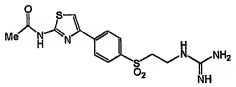
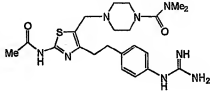
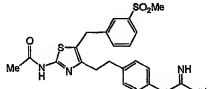
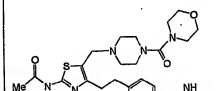
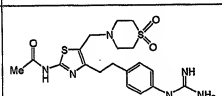
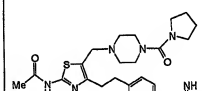
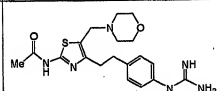
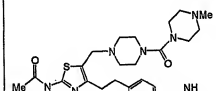
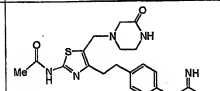
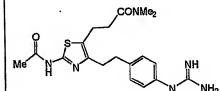
111	 HCl	116	 2HCl
112	 HCl	117	 2HCl
113	 2HCl	118	 2HCl
114	 2HCl	119	 3HCl
115	 2HCl	120	 HCl

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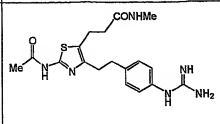
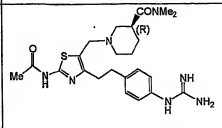
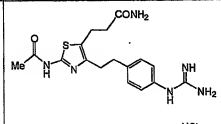
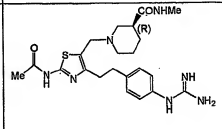
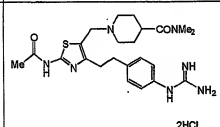
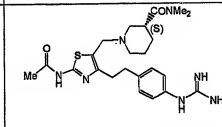
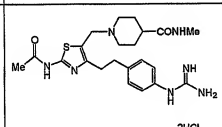
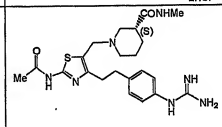
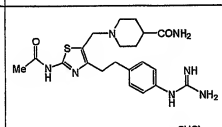
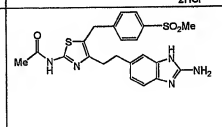
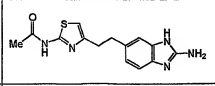
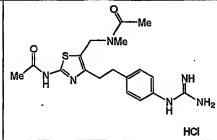
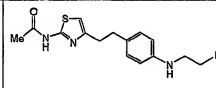
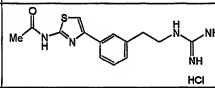
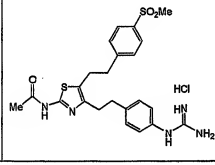
121	 HCl	126	 2HCl
122	 HCl	127	 2HCl
123	 2HCl	128	 2HCl
124	 2HCl	129	 2HCl
125	 2HCl	130	

No.	Structure
131	
132	 HCl
133	 2HCl
134	 HCl
135	 HCl

Example 1

Inhibitory Effect of Compound A on VAP-1 enzyme (SSAO) activity in human and rat plasma.

VAP-1 enzyme (SSAO) activity in both human and rat plasma was determined by a radiochemical-enzyme assay using ^{14}C-benzylamine as artificial substrate. The enzyme suspension prepared from blood plasma was pre-incubated with Compound A in 96-well microplate at room temperature for 30 min. The enzyme suspension was then incubated with ^{14}C-benzylamine ($2x10^{-5}$ mol/l final concentration) in a final volume of 50 µl at 37°C for 1 hour. The enzyme reaction was terminated by adding 2 mol/l (50 µl) citric acid. The oxidized products were directly extracted into a 200 µl toluene scintillator, and its radioactivity was measured by a scintillation spectrometer. Monoamine oxidase (MAO) and diamine oxidase (DAO, histaminase) activities were also determined by similar method using ^{14}C-phenylethylamine and ^{14}C-putrescine as substrate, respectively. Cloned DAO from cDNA libraries was used in human DAO assay. Inhibition activity was expressed as IC_{50} (µmol/l) value.

Compound A completely inhibited the enzyme activity of human and rat plasma SSAO, but not the enzyme activities of other amine oxidases, such as human platelet MAO and cloned DAO, shown in Table 1.

Table 1. Inhibitory effect (IC_{50} values, µM) of Compound A on various amine oxidase activities

Human plasma SSAO	Rat plasma SSAO	Human platelet MAO	Cloned human DAO
0.15	0.012	>100	>100

Example 2

Effect of Compound A on ocular permeability in diabetic rats.

Diabetes in rats was induced with an intraperitoneal

(i.p.) injection of 65 mg/ml/kg of streptozotocin (STZ) in 2 mmol/l citrate buffer (pH 4.5) after a 20-h fast. At the same time control rats were injected with an equal volume of 2 mmol/l citrate buffer. Plasma glucose level was checked by a colorimetric method. At day 3 of STZ treatment, the rats were diagnosed with diabetes showing a plasma glucose level of 350 mg/dl.

The treatment of Compound A was given daily from 2 weeks after STZ treatment for 2 weeks. At 24 hrs after final treatment of Compound A, the vascular permeability in oculus was investigated based on the leakage of dye into the vitreous 30 min after intravenous injection of fluorescein solution (40 mg/ml/kg). Permeability was expressed as vitreous/plasma ratio of fluorescein concentration measured by a fluorophotometer. At the same time, the plasma SSAO activity was checked by the radiochemical-enzyme assay using ^{14}C-benzylamine ($2x10^{-5}$ mol/l final concentration) as substrate.

The significant increase of ocular permeability in diabetic rats was examined at 4 weeks after treatment of STZ and compared with that of normoglycemic normal rats. The treatment of Compound A (10 mg/kg, s.c. u.i.d.) given daily from 2 weeks after STZ treatment improved the ocular permeability, in comparison with the STZ control group (Table 2). Plasma SSAO enzyme activity also increased in diabetic rats at 4 weeks after STZ treatment, but the treatment with Compound A exhibited dose-dependent inhibition of the increased plasma SSAO activity (Table 3).

Table 2. Vitreous/Plasma Ratio of Fluorescein Concentration ($x10^{-3}$)

Normal	STZ control	Compound A treatment
3.30 ± 0.38**	8.93 ± 1.14	5.39 ± 0.73**

Values are mean ± S.E.M.s for 10 rats. **p<0.01 vs corresponding value for STZ control by Dunnett's test.

Table 3. Plasma SSAO activity (pmol/min/ml)

Normal	STZ control	Compound A treatment
4.40 ± 0.34**	10.0 ± 0.73	2.51 ± 0.26**

Values are mean ± S.E.M.s for 10 rats. **p<0.01 vs corresponding value for STZ control by Dunnett's test.

Example 3

In the same manner as in Example 2, the effect of various VAP-1 inhibitors on ocular permeability was determined in diabetic rats.

The treatment of Compund B (0.003%, ocular instillation, u.i.d. and 0.1 mg/kg, s.c., respectively) given daily from 2 weeks after STZ treatment improved the ocular permeability, in comparison with the STZ control group (Table 4).

Table 4. Vitreous/Plasma Ratio of Fluorescein Concentration ($x10^{-3}$)

Compound	Normal	STZ control	Compound treatment
Compund B 0.003%, ocular instillation	6.75±0.63**	14.8±0.77	9.86±1.65*
Compund B 0.1 mg/kg, s.c.	9.30±0.66**	15.6±1.16	7.54±0.80**

Values are mean ± S.E.M.s for 10 rats. **p<0.01 vs corresponding value for STZ control by Dunnett's test.

Example 4

Effect of eye-drop instillation with Compound A on increased retinal VAP-1 activity in STZ diabetic rats.

A 0.1% solution of Compound A was instilled into the eyes of STZ diabetic rats (10 µl/eye) prepared in the same manner as in Example 2. To the normal group and STZ control group, a vehicle was instilled. At 6 hours from the instillation, the retina was removed from the animals and the retinal VAP-1 activity was determined.

Compound A completely inhibited the increased retinal VAP-1 activity in STZ diabetic rats, shown in Table 5.

Table 5. Retinal VAP-1 activity (pmol/min/mg protein)

Compound	Normal	STZ control	Compound A treatment
Compound A 0.1%, ocular instillation	5.97±1.12	8.22±2.60	4.86±0.70

Values are mean ± S.E.M.s for 4 rats.

Example 5

Effect of Compound A on increased retinal VEGF level in STZ diabetic rats.

STZ diabetic rats were prepared in the same manner as in Example 2. Compound A (0.1 mg/kg, sc, u.i.d.) was administered from 3 days to 8 weeks after the STZ administration. To the normal group and STZ control group, a vehicle was treated. At 8 weeks from the STZ administration, the retina was removed from the animals and the retinal VEGF level was determined using a Murine VEGF ELISA kit.

Compound A completely inhibited the increased retinal VEGF level in STZ diabetic rats, shown in Table 6.

Table 6. Retinal VEGF level (pg/mg protein)

Compound	Normal	STZ control	Compound A treatment
Compound A 0.1 mg/kg, sc, u.i.d.	33.4±1.95*	42.7±3.47	28.3±2.72**

Values are mean ± S.E.M.s for 10 rats. *$p<0.05$, **$p<0.01$ vs corresponding value for STZ control by Dunnett's test.

The above result indicates that VAP-1 inhibitor is useful for treating a vascular hyperpermeable disease (except macular edema).

This application is based on application No. 60/458,370 filed in the United States of America, the content of which is incorporated hereinto by reference.

CLAIMS

1. A method for treating a vascular hyperpermeable disease (except macular edema), which method comprises administering to a subject in need thereof a vascular adhesion protein-1 (VAP-1) inhibitor in an amount sufficient to treat said subject for said disease.

2. The method of claim 1, wherein said disease is a disease in mucous membrane.

3. The method of claim 2, wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or respiratory tract.

4. The method of claim 1, wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic operation, an ocular inflammatory disease caused by a physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis,

angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

5. The method of claim 1, wherein the VAP-1 inhibitor is a compound of the formula (I):

$$R^1—NH—X—Y—Z \quad (I)$$

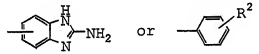
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:

 or

wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$; and

E is optionally protected amino, $-N=CH_2$,

 or 

wherein

Q is -S- or -NH-; and

R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

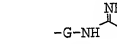
or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

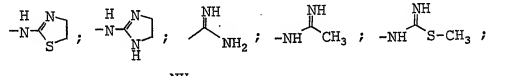
6. The method of claim 5, wherein, in the formula (I), Z is a

group of the formula:

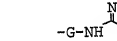
wherein R^2 is a group of the formula:



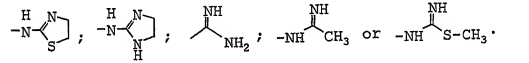
(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



7. The method of claim 6, wherein, in the formula (I), R^2 is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



8. The method of any of claims 5 to 7, wherein, in the formula (I), R^1 is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl.

9. The method of claim 1, wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

10. The method of claim 1, wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition for the treatment of a vascular hyperpermeable disease (except macular edema), which comprises, as an active ingredient, a VAP-1 inhibitor.

12. The composition of claim 11, wherein said disease is a disease in mucous membrane.

13. The composition of claim 12, wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or respiratory tract.

14. The composition of claim 11, wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema,

diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic operation, an ocular inflammatory disease caused by a physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis, angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

15. The composition of claim 11, wherein the VAP-1 inhibitor is a compound of the formula (I):

$$R^1—NH—X—Y—Z \quad (I)$$

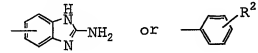
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:



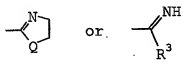
wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$; and

E is optionally protected amino, $-N=CH_2$,



wherein

Q is -S- or -NH-; and

R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

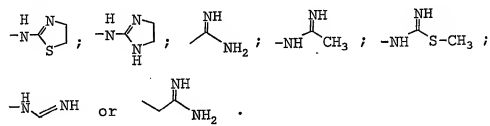
or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

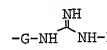
16. The composition of claim 15, wherein, in the formula (I), Z is a group of the formula:

wherein R^2 is a group of the formula:

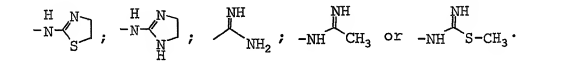
(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



17. The composition of claim 16, wherein, in the formula (I), R^2 is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



18. The composition of any of claims 15 to 17, wherein, in the formula (I), R^1 is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl.

19. The composition of claim 11, wherein the VAP-1 inhibitor is

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

20. The composition of claim 11, wherein the VAP-1 inhibitor is

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-

thiazol-2-yl}acetamide;
or a derivative thereof;
or a pharmaceutically acceptable salt thereof.

21. A use of a VAP-1 inhibitor for preparing a medicament for the treatment of a vascular hyperpermeable disease (except macular edema).

22. The use of claim 21, wherein said disease is a disease in mucous membrane.

23. The use of claim 22, wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or respiratory tract.

24. The use of claim 21, wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic operation, an ocular inflammatory disease caused by a physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis,

angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

25. The use of claim 21, wherein the VAP-1 inhibitor is a compound of the formula (I):

$$R^1—NH—X—Y—Z \quad (I)$$

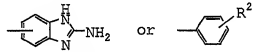
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:



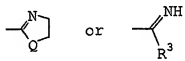
wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$; and

E is optionally protected amino, $-N=CH_2$,



wherein

Q is -S- or -NH-; and

R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

or a derivative thereof;

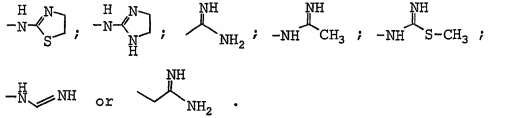
or a pharmaceutically acceptable salt thereof.

26. The use of claim 25, wherein, in the formula (I), Z is a

group of the formula:

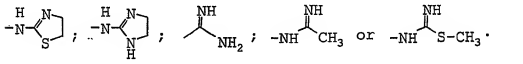
wherein R^2 is a group of the formula:

(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



27. The use of claim 26, wherein, in the formula (I), R^2 is a group of the formula:

(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



28. The use of any of claims 25 to 27, wherein, in the formula (I), R^1 is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl.

29. The use of claim 21, wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,
N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-

yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

30. The use of claim 21, wherein the VAP-1 inhibitor is

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2004/004596

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/426 A61P27/00 A61P17/00 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/02541 A (BIOTIE THERAPIES CORP ; JALKANEN MARKKU (FI); SMITH DAVID JOHN (FI); B) 10 January 2002 (2002-01-10) abstract page 7, line 21 - page 9, line 2	1-4, 11-14, 21-24
X	WO 02/02090 A (BIOTIE THERAPIES CORP ; JALKANEN MARKKU (FI); SMITH DAVID JOHN (FI); B) 10 January 2002 (2002-01-10) abstract page 8, line 9 - page 9, line 13	1-4, 11-14, 21-24
X	US 2002/173521 A1 (JALKANEN MARKKU ET AL) 21 November 2002 (2002-11-21) abstract paragraphs '0117!, '0118!	1-4, 11-14, 21-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2004	25/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
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X	WO 97/24343 A (BOEHRINGER INGELHEIM CA LTD ; BOEHRINGER INGELHEIM PHARMA (US)) 10 July 1997 (1997-07-10) abstract page 49, lines 1-16 page 116; examples 18,19; table 3 pages 159-161 page 201 page 238	1-6,8, 11-16, 18, 21-26,28
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X	WO 03/006003 A (BIOTIE THERAPIES CORP ; ALARANTA SAKARI (FI); VAINIO PETRI (FI); PIHLA) 23 January 2003 (2003-01-23) abstract page 10, line 19 - page 14, line 1	1-4, 11-14, 21-24
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 114 365 A (SALOM BARBARA ET AL) 5 September 2000 (2000-09-05) the whole document	1-30
A	EP 1 256 578 A (PFIZER PROD INC) 13 November 2002 (2002-11-13) the whole document	1-30

International application No.
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INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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